EXHIBIT 8

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

IN RE: JOHNSON & JOHNSON TALCUM POWDER PRODUCTS MARKETING, SALES PRACTICES AND PRODUCTS LIABILITY LITIGATION ***THIS DOCUMENT RELATES TO:*** ***Bondurant v. Johnson & Johnson*, No. 3:19-cv-14366** ***Converse v. Johnson & Johnson*, No. 3:18-cv-17586** ***Gallardo v. Johnson & Johnson*, No. 3:18-cv-10840** ***Judkins v. Johnson & Johnson*, No. 3:19-cv-12430** ***Newsome v. Johnson & Johnson*, No. 3:18-cv-17146** ***Rausa v. Johnson & Johnson*, No. 3:20-cv-02947**	**Civil Action No. 3:16-md-2738-MAS-RLS** **MDL No. 2738**

Date: May 28, 2024

Gregory B. Diette, M.D., M.H.S.

1. EXPERT DECLARATION OF GREGORY DIETTE, MD, MHS

SCOPE OF REPORT

I was retained by Johnson & Johnson, and LLT (f/k/a Johnson & Johnson Consumer Inc.) to review the epidemiological literature regarding the hypothesized connection between talc containing certain constituents and the development of ovarian cancer. I understand that plaintiffs in this proceeding allege that exposure to talcum powder products containing asbestos (or other constituent parts) poses an ovarian cancer risk. I further understand that Johnson & Johnson disputes that its talcum powder contains asbestos or other carcinogens. It is my opinion, to a reasonable degree of scientific certainty, that the science does not support an ovarian cancer risk from exposure to talcum powder products, even if those products were to contain trace amounts of asbestos.

MY QUALIFICATIONS

I am a professor of medicine at the Johns Hopkins University School of Medicine. I hold joint appointments in the Departments of Environmental Health Sciences and Epidemiology in the Johns Hopkins Bloomberg School of Public Health.

I received my M.D. from the Temple University School of Medicine. I completed my residency at the Hospital of the University of Pennsylvania and performed a fellowship in pulmonary and critical care medicine at Johns Hopkins. I received my M.H.S. in Epidemiology and Clinical Epidemiology from the Johns Hopkins Bloomberg School of Public Health. Currently, I am an attending physician at the Johns Hopkins Hospital and the Johns Hopkins Bayview Medical Center, practicing both inpatient and outpatient care.

My areas of clinical expertise include internal medicine, pulmonary medicine and critical care medicine. My areas of research include environmental impacts on lung disease and epidemiology of chronic diseases. I have published more than 200 studies in peer-reviewed journals on a variety of medical and scientific subjects, including the epidemiological study of disease causation, disease risk factors and gene expression, as well as the health effects of environmental pollutants. In addition, I am a peer reviewer for a number of journals. I have also repeatedly lectured and instructed on advanced research methods in epidemiology.

I currently hold multiple positions related to teaching and clinical research. I am an attending physician at Johns Hopkins and a member of the American Thoracic Society, where I served on the Board of Directors and have participated in a number of its teaching programs, including the Methods in Epidemiologic, Clinical and Operations Research program. I also previously served as the Director of Clinical Research in the Division of Pulmonary and Critical Care Medicine for almost 14 years.

Additional information pertaining to my background and qualifications can be ascertained from my curriculum vitae, which is attached to this report, together with other required disclosures. I am being compensated at a rate of $600 per hour for my work on this case and $775 per hour for testimony.

SUMMARY OF OPINIONS

The body of relevant epidemiological evidence does not support a causal connection between perineal use of cosmetic talcum powder products (whatever constituents those products may contain in addition to talc) and ovarian cancer.[1] As fully set forth below:

- The epidemiological literature shows a non-existent association or, at most, a small association between perineal talc use and ovarian cancer (including borderline serous OC) that constitutes only weak epidemiological evidence. Because any purported association reported in the literature is weak, it may well be attributed to factors such as confounding, bias or chance.

- Studies have not consistently shown an association. The prospective epidemiological studies (cohort studies) do not show a statistically significant association; the hospital-based case-control studies do not show a statistically significant association; and only a subset of the population-based case-control studies show a statistically significant association. If consistency could be drawn from these inconsistent results, it would be a consistency of null results because case-control studies, which are more easily subject to certain biases and confounding factors, are not the best evidence for proving causation.

- Evidence of a dose-response relationship is lacking. None of the cohort studies reveals a dose-response relationship, and only a handful of case-control studies, including those analyzing "cumulative" talc use, have purported to find one. Moreover, study authors and plaintiffs' experts all agree that there are major challenges to interpreting the study findings on dose-response because there can be no assurance that any estimates of talc use are accurate or valid. Indeed, there is not a single epidemiologic study of ovarian cancer and talcum powder that has used, or claims to have used, a validated measure of talcum powder use. Without a validated measure of talcum powder use, it is impossible to correctly determine whether or not an exposure occurred or the quantity of purported exposure, casting considerable doubt on any purported causative relationship between perineal talcum powder use and ovarian cancer.

- The theories as to how talc or asbestos would reach the ovaries have not been validated, and the scientific community has repeatedly expressed the opinion that the potential mechanism by which talcum powder is associated with ovarian cancer remains speculative.

- Additional Bradford Hill factors – temporality, coherence of the association and analogy – are not satisfied based on the available epidemiologic evidence and do

[1] Plaintiffs' expert, Dr. Smith-Bindman, states in her report that there are "hundreds of different constituents" within cosmetic talc powder, many of which have been designated Group 1 carcinogens by the International Agency for Research on Cancer ("IARC"), but IARC categorized cosmetic talc under Group 2b, including all the "constituents and ingredients" to which Dr. Smith-Bindman alludes. Smith-Bindman 2nd Am. Rep. at 11.

not support the allegation that talcum powder use can cause ovarian cancer.

- To the extent plaintiffs' experts opine that asbestos is an accessory mineral present in cosmetic talc that causes ovarian cancer, this theory would not alter the analysis because the existing epidemiological literature regarding perineal talc use would necessarily account for the presence of any asbestos in the products used in those studies. Plaintiffs' experts' asbestos-based theories are also problematic due to the lack of a plausible mechanism by which asbestos could reach the ovaries and a lack of any reliable epidemiology supporting such a causal connection.

- I have reviewed the available radiology films and related records outlined in Appendix B of this report, and based on my experience as a pulmonologist, there is no evidence of markers of asbestos exposure, such as pleural plaques, diffuse pleural thickening or asbestosis in the available films for any of the six bellwether plaintiffs.

- Since this litigation began, the science has developed in a way that further calls into question the causal hypotheses asserted by plaintiffs' experts. The most recent pooled analysis of cohort studies debunked any causal connection between perineal talc exposure and ovarian cancer. Moreover, plaintiffs' experts' further attempts to manufacture a plausible biological mechanism using *in vitro* data from studies connected to litigation are troubling.

APPROACH

Bradford Hill Framework

Epidemiologists and other scientists are often tasked with determining whether or not an exposure can cause an illness or condition. After an association has been demonstrated, criteria articulated by Austin Bradford Hill in a lecture in 1965 are often employed. These Bradford Hill considerations, or criteria, are considered the gold standard for assessing causation based on observed associations. The nine considerations are: consistency, strength of association, specificity, dose-response relationship, temporality, biologic plausibility, coherence of the association, analogy and experimentation.[2] In applying these criteria, an epidemiologist should consider all available evidence, which can be assessed and graded according to its sufficiency (or lack thereof) to establish a causal link. Evidence typically comes from research studies that involve humans, but it can also include well-designed studies of animals or in vitro systems (toxicological and experimental) to provide supportive evidence, especially for plausibility.

Another useful factor for assessing causation is consideration of non-causal explanations for the results of individual studies.[3] As explained further below, these other explanations can come from bias, confounding and chance. For example, drinking coffee might be correlated with

[2] Hill AB. The Environment and Disease: Association or Causation? *Proceedings of the Royal Society of Medicine.* 1965;58(5):295-300 ("Hill 1965").

[3] Elwood JM. "The diagnosis of causation." Chapter 8 in *Causal Relationships in Medicine: A Practical System for Critical Appraisal.* (New York, NY: Oxford University Press, 1988). 163-182.

a higher risk of lung cancer, but the cause of the additional cases of lung cancer among individuals who drink coffee would be smoking cigarettes. In this example, the obvious confounding factor is that individuals who drink coffee are more likely to smoke. But confounding factors are not always identifiable, even after extended study, and these and other factors can consistently drive statistical associations that are not causal in nature. Such limitations can be quite important, as they can lead to risk estimates that are falsely higher or lower than actual risk, and they can even lead to the conclusion that an exposure causes a disease when it does not, and vice versa.

Methodology

I was asked to assess whether perineal exposure to talcum powder causes ovarian cancer. Based on my extensive qualifications and experience, review of the available studies and data and assessment of the Bradford Hill factors, I conclude that the observations and evidence to date are insufficient to find a causal relationship between perineal exposure to talcum powder (inclusive of the constituents that might be found in talcum powder) and ovarian cancer.

My opinions are based on a review of the epidemiology literature relevant to the evaluation of the association between perineal talcum powder use and ovarian cancer. In my review, I considered case-control studies, prospective cohort studies and meta-analyses. I did not consider randomized trial data since I am not aware of any such data reporting on the presence or absence of an association between perineal use of talcum powder and ovarian cancer. Because the accuracy of the findings of case-control and cohort studies can be influenced by bias and confounders, I carefully considered whether there was any indication that these sorts of errors affected the results.

In evaluating the epidemiologic data and other scientific evidence under the Bradford Hill framework, I primarily focus on whether the criteria of strength of association, consistency of the association, biologic gradient (or dose-response) and biologic plausibility have been met. Although it is not essential to address every factor under the Bradford Hill framework, as some of plaintiffs' experts acknowledge,[4] I also address specificity, temporality, coherence of the association, experiment and analogy.

Lastly, I reviewed the reports submitted by plaintiffs' experts and their prior testimony. Some of these experts claim to have analyzed the Bradford Hill criteria and to have concluded through these analyses that perineal talc use causes ovarian cancer. I assess and address these experts' methods and analyses in this regard.

STUDY DESIGNS

Epidemiologists recognize that there is a hierarchy of evidence with respect to human studies. Clinical trials are often considered the strongest type of evidence, followed by

[4] E.g., Smith-Bindman 2nd Am. Rep. at 32; McTiernan 2nd Am. Rep. at 29; Siemiatycki 2nd Am. Rep. at 19-20; Harlow & Rothman at 4-5

observational studies (cohort and case-control). The lowest quality of evidence comes from case reports, case series and descriptive studies.[5]

There are two main types of epidemiological studies at issue here: prospective cohort studies and case-control studies.

Prospective cohort studies consist of identifying a large group of healthy individuals who differ in the key areas being observed and following them forward in time. Based on the data collected, it is determined how the factors of interest, e.g., exposure to talcum powder, are associated with a certain outcome or disease. Cohort studies are widely regarded as more reliable than retrospective case-control studies because they are not susceptible to recall bias, which is the propensity of study subjects with the disease that is being studied to report their exposure to the agent at issue inaccurately, a phenomenon that can generate inflated risk estimates.[6] Cohort studies generally avoid this pitfall because they are prospective rather than retrospective.[7] Due to the ability of cohort studies to assess exposure at baseline instead of relying solely on recall, they can be better suited to detect risks from exposure to an agent.

In case-control studies, individuals with the disease of interest (cases) and those without the disease of interest (controls) are first identified. These two groups are then compared to assess any differences between them regarding a specified exposure. Case-control studies can be further broken down into population-based and hospital-based studies. Hospital-based studies draw their control population from patients who are hospitalized with conditions other than the one under study. Population-based studies draw study participants from the general population.

REVIEW OF EPIDEMIOLOGY DATA

In forming my opinions, I employed search tools, including Medline and Google Scholar, to identify studies that examined the potential association between perineal talcum powder use and the development of ovarian cancer. I also reviewed the reference lists of individual studies and the meta-analyses to assemble a complete list of studies. Specifically, I first located and reviewed the relevant cohort studies, meta-analyses and case-control epidemiologic studies. I then reviewed how other medical experts or other professional organizations interpreted those studies. My reliance list, which is attached to this report, is comprised of all studies located and assessed specifically for this case. In total, I identified and reviewed 32 case-control studies and three prospective cohort studies published since 1982 that pertain to perineal talc use and ovarian cancer.

---

[5] Elwood 1988 at 174-175.

[6] Gertig DM, Hunter DJ, Cramer DW, et al. Prospective Study of Talc Use and Ovarian Cancer. *Journal of the National Cancer Institute.* 2000;92(3):249-252, at 252 ("Gertig 2000"); Langseth H, Hankinson SE, Siemiatycki J, Weiderpass E. Perineal Use of Talc and Risk of Ovarian Cancer. *Journal of Epidemiology and Community Health.* 2008;62(4):358-360, at 358 ("Langseth 2008"). *See generally* Leon Gordis. Epidemiology. 6th ed. Philadelphia, PA: 2019.

[7] Although there are also retrospective cohort studies, those are not at issue here, because the cohort studies involving cosmetic talc use are prospective in design.

It is my understanding that plaintiffs are asserting that cosmetic talc products can contain asbestos. The epidemiological literature concerning talc products and ovarian cancer generally has not attempted to investigate the question whether asbestos is present in talc as an accessory mineral. Nevertheless, if talc products have generally contained asbestos, the epidemiological literature would reflect the risks posed by any asbestos in talc and/or any alleged risk of other constituent parts.

The Strength Of Association In The Relevant Body Of Epidemiology Is Weak.

The first Bradford Hill criterion, strength of the association, refers to the magnitude of the risk of developing a given outcome in the presence of a measured risk factor. In the studies discussed in this report, risk is reported in various ways – as a relative risk ("RR"), odds ratio ("OR"), or hazard ratio ("HR") – typically with a confidence internal ("CI"). A relative risk "of an event is the likelihood of its occurrence after exposure to a risk variable" – here, talcum powder or asbestos – "as compared with the likelihood of its occurrence in a control or reference group."[8] An odds ratio is "a comparison of the odds of an event after exposure to a risk factor with the odds of that event in a control or reference situation."[9] A hazard ratio is a type of relative risk that measures "how often a particular event happens in one group compared to how often it happens in another group, over time."[10] In each case, the risk is expressed as a number for which 1 is the denominator, so that a relative risk of 1.3, for example, would mean that the outcome of interest occurred 1.3 times as often in the exposed group as compared to the control group – a 30% greater incidence. A relative risk of 1.0, by contrast, would mean there was no difference. It is important to recognize that a relative risk is not the same as attributable risk; it tells us nothing about how much to attribute the occurrence of a disease in an individual to a given factor, nor what proportion of a disease's population incidence is explained by the risk factor. This is a common misconception by untrained scientists but I have seen it made by some plaintiffs' experts as well.[11] Despite her epidemiology credentials, Dr. Smith-Bindman appears to have made an even more elementary error, suggesting that every single cancer case in an exposed subject must be attributable to the exposure simply because there is an elevated relative risk.[12]

In each case, a confidence interval can be calculated to determine statistical significance – in essence, whether the difference between the exposed and unexposed groups is likely to persist if the same study were repeated. When a confidence interval contains 1.0, the result is deemed not to be statistically significant because the possibility that there is no real association is within the expected range of results. It is typical to calculate a 95% confidence interval,

---

8 Andrade C. Understanding Relative Risk, Odds Ratio, and Related Terms. *The Journal of Clinical Psychiatry.* 2015;76(7):e857-861.

9 *Id.*

10 National Cancer Inst., NCI Dictionary of Cancer Terms, "hazard ratio," https://www.cancer.gov/publications/dictionaries/cancer-terms/def/hazard-ratio.

11 *See* 3/8/2024 Clarke-Pearson Dep. 284:10-285:1; *see also id.* 332:17-333:1.

12 *See* Smith-Bindman 2d Am. Rep. at 34.

expressed in this report as "95% CI," meaning that if the study were repeated, the results would be expected to fall within the confidence interval 95% of the time.

While there is no absolute cutoff to define a large versus a small relative risk, Dr. Hill provided examples of large risks, including the 200 times risk of scrotal cancer in chimney sweeps, an estimate of 9-10 times risk of lung cancer in smokers and 20-30 times risk of lung cancer in heavy smokers. As an example of a low risk, Dr. Hill used death from coronary thrombosis in smokers, which he described as "no more than twice, probably less" than the death rate in non-smokers ["twice" would be reflected as a relative risk of 2.0]. Dr. Hill further explained:

> "[T]hough there is good evidence to support causation it is surely much easier in this case to think of some features of life that may go hand in hand with smoking—features that might conceivably be the real underlying cause or, at the least, an important contributor, whether it be lack of exercise, nature of diet or other factors. But to explain the pronounced excess in cancer of the lung in any other environmental terms requires some feature of life so intimately linked with cigarette smoking and with the amount of smoking that such a feature should be easily detectable."[13]

What this passage from Hill means is that low observed risks are more likely to be non-causal than higher risk ratios, because the effects of distorting factors (such as confounders and bias) have a greater chance of being the true explanation for the observations. Because very small risks are highly susceptible to distorting effects in observational studies, further evidence is required to demonstrate that the purported association did not arise from bias, confounding or chance alone. Plaintiffs' experts express opinions about risks that they characterize as approximately a 1.3-1.5 odds ratio.[14] This is considered a weak association by the scientific community, as some of plaintiffs' own experts in the talc litigation have acknowledged.[15] To the extent other plaintiffs' experts dispute this point, their position is simply not credible. While the size of the risk does not, in itself, determine causation, this purported low risk estimate is not strong evidence of causation. As Dr. Jack Siemiatycki, an expert for plaintiffs, wrote in a 1988 article, "[s]mall excess relative risks, even if they are statistically significant, are often interpreted with great caution, if not skepticism."[16]

---

[13] Hill 1965.

[14] Plunkett 2nd Am. Rep. at 55; Smith-Bindman 2nd Am. Rep. at 30, 34; Wolf 2nd Am. Rep. at 17; McTiernan 2nd Am. Rep. at 88-89; Clarke-Pearson 2nd Am. Rep. at 13; Siemiatycki 2nd Am. Rep. at 1; Cote Rep. at 5 Singh Supp. Rep. at 19.

[15] Plunkett Oct. 5, 2016 Rep. at 17 (acknowledging that "this increase in risk identified in the scientific literature reports is not large"); Singh Dep. 140:19-25 (agreeing that scientific literature does not consider 1.3 a strong association); Singh Supp. Rep. at 19 (noting risks are "of modest magnitude").

[16] Siemiatycki J, Wacholder S, Dewar R, et al. Degree of confounding bias related to smoking, ethnic group, and socioeconomic status in estimates of the associations between occupation and cancer. *Journal of Occupational and Environmental Medicine.* 1988;30(8): 17–625.

Results Of Cohort Studies, Case-Control Studies, Meta-Analyses And Pooled Studies

As fully set forth in the next sections, the prospective epidemiological studies (cohort studies) do not show a statistically significant association between genital talc use and ovarian cancer, while a subset of the population-based case-control studies do show weak statistically significant associations.

Results of Cohort Studies

The results of the first cohort study that considered the possible association between perineal talc use and ovarian cancer, the Nurses' Health Study ("NHS") were published in 2000[17] and updated in another publication ten years later.[18] NHS was a prospective cohort of 121,700 registered nurses in the United States established in 1976.[19] The Gertig analysis, published in 2000, showed no statistically significant association between perineal talc use (RR 1.09 (95% CI: 0.86-1.37)), use of talc on sanitary napkins (RR 0.89 (95% CI: 0.61-1.28)) and for both uses combined (RR 0.90 (95% CI: 0.59-1.37)).[20] It further showed no statistically significant association for various different frequencies of use and no indication that risk increased with more frequent use: less than one use per week (RR 1.14 (95% CI: 0.81-1.59)); 1-6 uses per week (RR 0.99 (95% CI: 0.67-1.46)); daily use (RR 1.12 (95% CI: 0.82-1.55)).[21] When examining the results by histology, the authors observed a weak statistically significant association for serous invasive (RR 1.40 (95% CI: 1.02-1.91)) but no other types of ovarian cancer.[22] The authors noted that perineal talc use "may modestly increase the risk of invasive serous ovarian cancers" but not "all serous cancers (including borderline cancers), endometrioid cancers, or mucinous cancers," and concluded overall that their "results provide little support for any substantial association between perineal talc use and ovarian cancer risk."[23]

The 2010 Gates report, which followed up on the NHS cohort ten years later (by which time the women were 60-85 years old), found no statistically significant elevations in risk for talc use for all epithelial ovarian cancers (RR 1.06 (95% CI: 0.89-1.28)), serous invasive ovarian cancers (RR 1.06 (95% CI: 0.84-1.35)), endometrioid ovarian cancers (RR 1.06 (95% CI: 0.66-1.69)), or mucinous ovarian cancers (RR 1.50 (95% CI: 0.84-2.66)).[24] In other words, with further passage of time (i.e., longer follow-up of the cohort), the weak association for the serous invasive type of ovarian cancer that was reported in Gertig disappeared. The authors concluded

---

17 Gertig 2000.

18 Gates MA, Rosner BA, Hecht JL, Tworoger SS. Risk Factors for Epithelial Ovarian Cancer by Histologic Subtype. *American Journal of Epidemiology.* 2010;171(1):45-53, at 50 ("Gates 2010").

19 Gertig 2000.

20 *Id.* at 251.

21 *Id.*

22 *Id.*

23 *Id.* at 250-51.

24 Gates 2010 at 50.

that their results for talc exposure "generally are consistent with the existing literature," i.e., consistent with generally null and/or weakly associated results.[25]

Plaintiffs' experts' argument that the Gates report should be disregarded because the participants in the NHS were only asked about talcum powder use once is unfounded.[26] Ten additional years of follow-up is valuable data regardless of whether further questioning regarding talc use took place. Moreover, as other studies indicate, for women who are ever-users of perineal talcum powder, the mean duration of use is greater than 20 years[27] and the vast majority of women who use talcum powder initiate use before age 36.[28] That means that, even though the participants were only asked about their talcum powder use once, the data collected on perineal talcum powder application would have likely reflected chronic, habitual use. For similar reasons, meta-analyses by Penninkilampi (relied on heavily by plaintiffs' experts)[29] and Taher[30] (discussed further below) are of questionable value in light of their omission of the findings reported by Gates, which are derived from a cohort study that found no statistically significant elevations in risk for talc users with respect to epithelial ovarian cancers, serous invasive ovarian cancers, endometrioid ovarian cancers or mucinous ovarian cancers.

A second cohort study known as the Women's Health Initiative (or "WHI") Study followed 61,576 women for a mean of 12.4 years, at which point the women were, on average, 75.7 years old.[31] The study showed no increased risk of ovarian cancer from genital use of talc (HR 1.12 (95% CI: 0.92-1.36)), no increased risk of ovarian cancer from genital talc use for 10 or more years (HR 0.98 (95% CI: 0.75-1.29)) or 20 or more years (HR 1.10 (95% CI: 0.82-1.48)), and no increased risk of ovarian cancer with talc use on sanitary napkins (HR 0.95 (95% CI: 0.76-1.20)) or contraceptive diaphragms (HR 0.92 (95% CI: 0.68-1.23)).[32] The result for combined powder use was a statistically non-significant hazard ratio (HR 1.06 (95% CI: 0.87-

---

[25] *Id.* at 51. While the 2010 NHS expanded the number of women studied, the new participants were not asked about talc use until 2013.

[26] Smith-Bindman 2nd Am. Rep. at 19-20; Singh Supp. Rep. at 16.

[27] Wu AH, Pearce CL, Tseng CC, Pike MC. African Americans and Hispanics Remain at Lower Risk of Ovarian Cancer Than Non-Hispanic Whites after Considering Nongenetic Risk Factors and Oophorectomy Rates. Cancer Epidemiol Biomarkers Prev. 2015; 24(7):1094-100 ("Wu 2015").

[28] Gates MA, Tworoger SS, Terry KL, et al. Talc use, variants of the GSTM1, GSTT1, and NAT2 genes, and risk of epithelial ovarian cancer. Cancer Epidemiol Biomarkers Prev. 2008; 17(9):2436-2444 ("Gates 2008"); *see also* Cramer DW, Vitonis AF, Terry KL, et al. The Association Between Talc Use and Ovarian Cancer: A Retrospective Case-Control Study in Two US States. *Epidemiology*. 2016;27(3):334-346 ("Cramer 2016") at 335 ("The average age women began using talc was 20.0 for cases and 19.8 for controls.").

[29] Penninkilampi R, Eslick GD. Perineal Talc Use and Ovarian Cancer: A Systematic Review and Meta-Analysis. *Epidemiology*. 2018;29(1):41-49, at 44 ("Penninkilampi 2018"); McTiernan 2nd Am. Rep. at 56-58 ("In my opinion, the results of this 2018 meta-analysis give strong support for an association . . ."); Smith-Bindman 2nd Am. Rep. at 26-27 ("This comprehensive systematic review . . . ."); Wolf 2nd Am. Rep. at 9-10 (detailing the Penninkilampi findings and touting the favorable reception of the article by another author).

[30] Taher MK, Farhat N, Karyakina NA, et al. Critical Review of the Association Between Perineal Use of Talc Powder and Risk of Ovarian Cancer. *Reproductive Toxicology*. 2019;90:88-101 ("Taher 2019").

[31] Houghton SC, Reeves KW, Hankinson SE, et al. Perineal Powder Use and Risk of Ovarian Cancer. *Journal of the National Cancer Institute* 2014;106(9):dju208. ("Houghton 2014").

[32] *Id.*

1.28)) and an even lower statistically non-significant hazard ratio for combined use for more than ten years (HR 1.02 (95% CI: 0.80-1.30)).[33] The authors concluded that "perineal powder use does not appear to influence ovarian cancer risk."[34]

Another cohort study, referred to by many as the "Sister Study," enrolled 50,884 women in the U.S. and Puerto Rico beginning in 2003, who had a sister diagnosed with breast cancer, and followed 41,654 of those women for a median 6.5 years.[35] The study identified 154 cases of ovarian cancer and found no association between the use of talc and ovarian cancer – in fact, there was an inverse association that was not statistically significant (HR 0.73 (95% CI: 0.44-1.2)).[36] Of note, this study separately found an association between douching and ovarian cancer, suggesting that douching (which sometimes accompanies perineal talc use) may be a confounding variable that has not sufficiently been accounted for in past studies.[37]

Most recently, O'Brien et al. published an article which considered, in addition to the originally collected exposure data, data from a retrospective follow-up questionnaire sent to participants in the Sister Study cohort between 2017 and 2019.[38] The follow-up questionnaire asked for additional details about potential timing of use of douche and genital talc. The authors state that the focus remained on ever versus never use of each product during the time prior to enrollment. The authors noted that data on intimate care product use "were sometimes contradictory or missing." Normally, a cohort study (unlike case control studies) is unaffected by recall bias. However, in this case, because of the use of a survey that now collected retrospective exposure data, recall bias became a concern. The study results very clearly show that such bias was in fact introduced. The calculated HR for ovarian cancer with genital talc use is null [HR 1.02 (95% CI: 0.79-1.33)] when exposure status was "fully prospective" as reported on the enrollment questionnaire. The same analysis which now used "mostly retrospective" data from the fourth follow-up questionnaire produced an elevated risk [HR 2.65 (95% CI: 1.91-3.70)]. This is an exquisitely clear demonstration of the effect of recall bias and adds to the evidence provided by Schildkraut 2016.[39] The timing of administration of the fourth follow up survey (2017-2019) was during the time of even more marked media attention to talcum powder litigation (due to publicity over this litigation) than the time period that showed recall bias in Schildkraut 2016.

---

33 *Id.*

34 *Id.*

35 Gonzalez NL, O'Brien KM, D'Aloisio AA, Sandler DP, Weinberg CR. Douching, Talc Use, and Risk of Ovarian Cancer. *Epidemiology*. 2016;27(6):797–802. ("Gonzalez 2016").

36 *Id.* at 800-802.

37 *Id.* at 800.

38 O'Brian KM, Wentzensen N, Ogunsina K, Weinberg CR, D'Aloisio AA, Edwards JK, Sandler DP. Intimate Care Products and Incidence of Hormone-Related Cancers: A Quantitative Bias Analysis. *Journal of Clinical Oncology.* 2024;00:1-15.

39 Schildkraut JM, Abbott SE, Alberg AJ, et al. Association between Body Powder Use and Ovarian Cancer: The African American Cancer Epidemiology Study (AACES). *Cancer Epidemiology, Biomarkers & Prevention*. 2016;25(10):1411-1417 ("Schildkraut 2016").

In the present study, recall bias is also clearer because the authors had access to data collected both prospectively and retrospectively from the same study participants. Based on this study finding, the effect of recall bias was as much as an 89% increase in reported talc use. O'Brien et al. conducted modeling exercises to examine the theoretical impact of recall bias, but these models cannot replace the actual data and study findings. They are useful, though, in showing that reported risks can vary from elevated (HR >1 and statistically significant) to null to even protective (HR <1 and statistically significant), depending on the degree of recall bias. With the degree of recall bias apparent in this study, the best estimate of the HR for ever use of genital talc may be null or even consistent with a strong and significant protective effect.

As noted above, the authors did find that some women's reported exposures were contradictory, depending on whether the women were reporting intimate care product use on the first or the fourth survey. For example, on both surveys, 34% of women reported not douching prior to enrollment, while 5% reported being a user (with consistency of age) on both. The remaining 61% had some degree of discordance. Similar findings for reported talc usage were found, with 51% having some degree of discordance between the first and fourth surveys. Clearly, this lack of reliable reporting can have important impacts on risk estimates. It is especially concerning, given that women with incident cancer were "overrepresented" in the group who initially reported never using intimate care products and did not complete the follow up survey.

An even more serious challenge to the validity of the retrospective results in O'Brien 2024 comes from the substantial number of women (approximately 25%) who did not respond to the follow-up questionnaire (i.e., the retrospective portion of the study). Overall, there were substantial data missing for reported douching (28%) and genital talc use (29%). This degree of missingness is quite concerning as it affects the most important exposures being examined in this paper. Imputation methods were employed, but it is concerning that the positive associations that were estimated after imputation are entirely a product of the imputed data. As noted above, when the analysis of genital talc and ovarian cancer was performed with only the actual existing prospective data, the HR is 1.02 (95% CI: 0.79-1.33). Only after the authors apply "correction" and "imputation" (that is, substituting the missing data with data that may or may not be true) is there a significant positive result (e.g., HR 1.82 (95% CI 1.36-2.43)). One should be quite skeptical when a result differs so markedly after application of statistical techniques retrospectively, especially when the degree of missingness for the key variables is so substantial.

I also note some puzzling decisions by the authors. The authors performed what they called a "correction for contradictory data." For respondents who reported use at enrollment but no use at follow up, the authors assumed 90% had been correct the first time and wrong the second time and classified them as talc users. For the respondents in the opposite contradictory group (i.e., those women who reported no talc use in their enrollment questionnaire, but then later reported in the follow up questionnaire that they had used talc during those periods, the authors assumed 80% had been wrong the first time and right the second time and classified them as talc users at enrollment. This second correction is contrary to the authors' prior work in which they stated that "because enrollment was more proximal to th[e] referent time period, we consider use reported on the enrollment questionnaire to be the 'gold standard.'" The authors do not explain why they chose to "correct" the overwhelming majority of contradictory data in the direction of talc exposure, and I am not aware of any data that would support that decision.

Following this first "correction," the point estimate was slightly elevated but remained nonsignificant (HR 1.17 (95% CI: 0.92-1.49)). Sophisticated statistical techniques, when applied after data collection is performed, are not a substitute for collection of complete, accurate, unbiased data.

The authors conducted a subgroup analysis, based on patency of the reproductive tract. The analysis included a group of women who only used genital talc after having had surgery that interrupted the reproductive tract (tubal ligation and/or hysterectomy). For women with a patent tract, the HR was 1.83 (95% CI: 1.36-2.46). For those only using genital talc after surgery, the HR is 1.70 (95% CI:0.86-3.37). Although the latter risk is not statistically significant, the HR of 1.7 is positive and nearly identical to that of the patent tract group. If one were to adopt the views of plaintiffs' experts in this litigation, who only look at the direction of the HR, and not whether it is statistically significant, this finding should be concerning because it would cast significant doubt on their entire biologic plausibility theory, which assumes that a patent reproductive tract is required to allow talc to migrate from the perineum to the ovaries.

The authors noted that unmeasured confounding could still be present, and I agree. I note, for example, that a very recently published paper from the same Sister Study cohort (Chang 2024) highlighted the complex relationships of multiple types of personal care products used by women, including hygiene products. In that study, the authors reported a "positive association" of beauty products with ovarian cancer. Beauty products included items that were distinct from hygiene products, and included, for example, lipstick, nail polish and nail polish remover. Beauty products had a strong association with ovarian cancer in Black women [HR 3.62 (95% CI: 1.55-8.46)]. Notably, in O'Brien 2024 use of douche and genital talc were more common in Black women, though no adjustment was performed for those products.

Importantly, a conclusion of the study authors is that "These results do not establish causality and do not implicate any specific cancer-inducing agent." I agree and note that this study, although very recently published, does not alter my judgment that the epidemiologic literature has not established that perineal talc use causes ovarian cancer. This point is emphasized by the authors, when they noted (in 2024) the need to still confirm "underlying biological mechanisms and causal agents." In short, I consider the findings generated by retrospective statistical techniques by O'Brien et al. (2024) to be highly speculative. And I put vastly more weight on the large number of epidemiological studies available that use actual, rather than imputed, data.

Plaintiff Expert Critiques Of Cohort Studies

Plaintiffs' experts offer several criticisms of the cohort studies. Drs. Smith-Bindman and McTiernan suggest that the cohort studies are limited because they "rarely focus on a single, narrowly defined question such as the association between regular use of talcum powder products and cancer" and instead ask "a broad range of questions."[40] This suggestion is wrong.

[40] Smith-Bindman 2nd Am. Rep. at 17; McTiernan 2nd Am. Rep. at 24 ("Because cohort studies typically are designed to look at multiple outcomes such as cancers, cardiovascular diseases, mortality, and other diseases, information collected on exposures tends to be minimal . . ."); *id.* at 25; *see also* Singh Supp. Rep. at 6 ("None of the cohort studies were designed to assess the risk of talc and ovarian cancer *a-priori*.").

The fact that cohort studies are able to study many variables and outcomes is an illustration of what is valuable and can be achieved with cohort studies. I know of no epidemiologists who believe that the results of cohort studies should be generally discounted due to this common design trait; indeed, such a view would conflict with the generally accepted principle that cohort studies can produce a higher level of evidence than case-control studies.

Plaintiffs' experts also contend that the cohort studies are limited in that they provide "poor, not specific, or inaccurate" measurements of exposure,[41] but this is equally true of case-control studies, as discussed herein. None of the epidemiological studies is able to quantify an "application" or "dose" of talcum powder regardless of frequency or duration of use.

Plaintiffs' expert Dr. McTiernan states that "[c]ohort studies may need to be very large (up to hundreds of thousands of participants) to have sufficient statistical power" to identify low risks.[42] This sentiment was echoed by other plaintiffs' experts as well.[43] However, this contention makes no sense because the data from the most recent pooled analysis of cohort studies collected information from more than 250,000 women, including more than 2,200 cases.[44] None of plaintiffs' experts conducted a power analysis on O'Brien 2020, and its robust analysis satisfies the mandates of an article on power oft-cited by plaintiffs' experts, Narod 2016.[45]

Plaintiffs' experts also criticize cohort studies for their follow-up periods, which they believe do not account for the latency period for ovarian cancer.[46] In light of the data noted above about mean initiation and duration of talc use, it is reasonable to assume that the date on which study participants were asked about their talcum powder use was not the date of first use and thus not the date that a true latency period would have begun. Moreover, the Women's Health Initiative Study asked about talcum powder use for 20-plus years and found no statistically significant increased risk in ovarian cancer after following those women for 12.4

---

[41] Smith-Bindman 2nd AM. Rep. at 17.; McTiernan 2nd Am. Rep. at 24 ("information collected on exposures tends to be minimal"); *id.* at 25 ("none of these [cohort] studies fully ascertained exposure to talc"); Wolf 2nd Am. Rep. at 8 ("All of the cohort studies are limited by . . . failure to make the appropriate inquiries"); Cote Rep. at 27 (cohort studies "did not have detailed exposure information"); Singh Supp. Rep. at 11 ("information on powder exposure is typically more limited in cohort studies").

[42] McTiernan 2nd Am. Rep. at 24.

[43] *See* Cote Rep. at 25 (stating that a disadvantage of "cohort design" "is that they "accrue fewer cases than a case-control study"); Smith-Bindman 2nd Am. Rep. at 17 ("The other disadvantage of cohort studies is that a very large number of patients must be assessed over a long period of time . . ."); Singh Supp. Rep. at 11 (listing "[l]imited statistical power" as negative of cohort studies); Wolf 2nd Am. Rep. at 8 ("All of the cohort studies are limited by lack of power.").

[44] O'Brien 2020 (Table 1).

[45] Wolf 2nd Am. Rep. at 6 ("Narod estimated that, for a cohort study to be properly powered to accurately predict the risk associated with talc use and ovarian cancer, as many as 200,000 women may be necessary."); Singh Supp. Rep. at 7 ("Narod et al. estimate that upward of 200,000 women would have to be enrolled in a cohort study to detect an effect of 1.2. None of the individual cohorts enrolled such a large number of women.").

[46] Wolf 2nd Am. Rep. at 8 ("All of the cohort studies are limited by . . . short follow-up."); Siemiatycki 2nd Am. Rep. at 63;

years (meaning at least 32.4 years of latency were factored in),[47] and the Sister Study enrolled women between the ages of 35-74 and followed up after 6 years.[48] The Sister Study also asked about talc use between the ages of 10 and 13 years (which was 22 to 64 years prior to enrollment) and found "no detectable effect of prepubertal talc use on risk."[49] Therefore, it is clear in the case of the WHI study, as well as the Sister Study, that substantial numbers of cohort study participants were using talcum powder for decades, long enough to put any serious concerns about latency to rest. This is all the more true because, as discussed below, a recent pooled analysis of cohort studies included several additional years of follow-up for each of the studies discussed above and still did not find an association between perineal talc use and the development of ovarian cancer.[50]

Any criticism of the studies that rests on the idea of a latency period is highly speculative anyway. For the reasons set out in this report, science has not even established a causal relationship between talc and ovarian cancer of any sort; far less has it established a latency effect or the duration of any such effect. There is simply no scientific basis for the suggestion by plaintiffs' expert Dr. Wolf that it takes "at least twenty years" for some unspecified degree of perineal talc exposure to cause ovarian cancer.[51]

Finally, plaintiffs' experts' criticisms of cohort studies are collectively suspect because they are so extensive when compared to their relatively muted criticisms for case-control studies, which, as I detail in the next sections, have significant weaknesses. For example, Dr. Smith-Bindman offers the highly general pronouncement that it is "simply not true" that cohort studies are generally more reliable than case-control studies.[52] She also devotes several pages of her report to lodging numerous criticisms of each study that reported on cohort data; although she mostly spares Gertig 2000 (which happens to be the one cohort study she believes supports her theory); she declares in summary fashion that there is nothing "meaningful" to be gleaned from any of the other cohort studies.[53] Yet, she provides no similar analysis of the strengths and weaknesses of the case-control studies, noting in the single paragraph in which she discusses them that there are "too many to dedicate a paragraph to summarizing the methods of each."[54] Similarly, Dr. Wolf discusses three case-control studies, declaring them to be "the most useful" study design "based on their size and quality of design" without an exposition of their weaknesses, while emphasizing perceived limitations in each of the individual cohort studies and adding in conclusion that "[a]ll of the cohort studies are limited by lack of power, failure to make

---

47 Houghton 2014 at 3.

48 Gonzalez 2016 at 797.

49 *Id.* at 801.

50 O'Brien 2020 added several years of additional follow-up time for each cohort included in its analysis, resulting in average follow-up times of 33.2 years for NHS-I; 9.6 years for SIS; and 17.4 years for WHI. Overall, the mean follow-up time for the more than 250,000 women included in O'Brien 2020 was 11.2 years.

51 Wolf 2nd Am. Rep. at 18.

52 Smith-Bindman 2nd Am. Rep. at 16.

53 Smith-Bindman 2nd Am. Rep. at 17, 19-21.

54 *Id.* at 30.

the appropriate queries, selection bias, and short follow-up."[55] To be sure, all observational studies have limitations, and the cohort studies here are no exception, but those limitations must be considered in light of the totality of the evidence, and the more significant limitations of the case-control study design.

In summary, none of the cohort studies found a statistically significant association between talc use and ovarian cancer.[56] The results from O'Brien 2020 – inclusive of additional cases and years of follow-up – similarly confirm that there is no causal link between talcum powder exposure and ovarian cancer. The fact that these studies have shown uniformly null results strongly undermines plaintiffs' experts' causation theories.

Results of Case-Control Studies

I have identified 25 population-based case-control studies addressing talc use and ovarian cancer. The following table sets forth these studies' findings with respect to the association between ever/never talc use and ovarian cancer:

Author, Year	**Ever/Never Results**
Cramer 1982[57]	RR 1.92 (95% CI: 1.27-2.89)
Harlow & Weiss 1989[58]	RR 1.10 (95% CI: 0.70-2.10)
Harlow 1992[59]	OR 1.50 (95% CI: 1.00-2.10)
Chen 1992[60]	RR 3.90 (95% CI: 0.90-10.6)
Cramer & Xu 1995[61]	OR 1.6 (95% CI: 1.2-2.10)
Purdie 1995[62]	OR 1.27 (95% CI: 1.04-1.54)
Chang & Risch 1997[63]	OR 1.42 (95% CI: 1.08-1.86)

[55] Wolf 2nd Am. Rep. at 78.

[56] Berge W, Mundt K, Luu H, Boffetta P. Genital Use of Talc and Risk of Ovarian Cancer: A Meta-Analysis. *European Journal of Cancer Prevention*. 2018;27(3):248-257, at 251 ("Berge 2018") (assigning a statistically insignificant 1.02 relative risk to the cohort studies in aggregate).

[57] Cramer DW, Welch WR, Scully RE, Wojciechowski CA. Ovarian cancer and talc: a case-control study. Cancer. 1982;50(2):372-376.

[58] Harlow BL, Weiss NS. A case-control study of borderline ovarian tumors: the influence of perineal exposure to talc. *American Journal of Epidemiology*. 1989;130(2):390-394.

[59] Harlow BL, Cramer DW, Bell DA, Welch WR. Perineal exposure to talc and ovarian cancer risk. *Obstetrics & Gynecology*. 1992;80(1):19-26 ("Harlow 1992").

[60] Chen Y, Wu PC, Lang JH, et al. Risk factors for epithelial ovarian cancer in Beijing, China. *International Journal of Epidemiology*. 1992;21(1):23-29.

[61] Cramer DW, Xu H. Epidemiologic evidence for uterine growth factors in the pathogenesis of ovarian cancer. *Annals of Epidemiology*. 1995; 5(4):310-314.

[62] Purdie D, Green A, Bain C, et al. Reproductive and other factors and risk of epithelial ovarian cancer: an Australian case-control study. Survey of Women's Health Study Group. *International Journal of Cancer*. 1995;62(6):678-684.

[63] Chang S, Risch HA. Perineal Talc Exposure and Risk of Ovarian Carcinoma. *Cancer*. 1997;79(12):2396-2401 ("Chang & Risch 1997").

Author, Year	Ever/Never Results
Cook 1997[64]	RR 1.60 (95% CI: 0.90-2.80)
Green 1997[65]	RR 1.30 (95% CI: 1.10-1.60)
Godard 1998[66]	RR 2.49 (95% CI: 0.94-6.58)
Cramer 1999[67]	OR 1.45 (95% CI: 0.97-2.18)
Ness 2000[68]	OR 1.50 (95% CI: 1.10-2.00)
Mills 2004[69]	OR 1.37 (95% CI: 1.02-1.85)
Cramer 2005[70]	OR 1.16 (95% CI: 0.90-1.49)
Jordan 2007[71]	OR 1.00 (95% CI: 0.40-2.10)
Gates 2008[72]	RR 1.36 (95% CI: 1.14-1.63)
Merritt 2008[73]	OR 1.17 (95% CI: 1.01-1.36)
Moorman 2009[74]	Afr. Am.: OR 1.19 (95% CI: 0.68-2.09) Caucasian: OR 1.04 (95% CI: 0.82-1.33)
Wu 2009[75]	RR 1.53 (95% CI: 1.13-2.09)
Rosenblatt 2011[76]	OR 1.27 (95% CI: 0.97-1.66)

[64] Cook LS, Kamb ML, Weiss NS. Perineal Powder Exposure and the Risk of Ovarian Cancer. *American Journal of Epidemiology*. 1997;145(5):459-465 ("Cook 1997").

[65] Green A, Purdie D, Bain C, et al. Tubal sterilisation, hysterectomy and decreased risk of ovarian cancer. Survey of Women's Health Study Group. *International Journal of Cancer*. 1997;71(6):948-951.

[66] Godard B, Foulkes WD, Provencher D, et al. Risk factors for familial and sporadic ovarian cancer among French Canadians: a case-control study. *American Journal of Obstetrics and Gynecology*. 1998;179(2):403-410.

[67] Cramer DW, Liberman RF, Titus-Ernstoff L, et al. Genital Talc Exposure and Risk of Ovarian Cancer. *International Journal of Cancer*. 1999;81(3):351-356 ("Cramer 1999").

[68] Ness RB, Grisso JA, Cottreau C, et al. Factors related to inflammation of the ovarian epithelium and risk of ovarian cancer. *Epidemiology*. 2000;11(2):111-117.

[69] Mills PK, Riordan DG, Cress RD, Young HA. Perineal talc exposure and epithelial ovarian cancer risk in the Central Valley of California. *International Journal of Cancer*. 2004;112(3):458-464 ("Mills 2004").

[70] Cramer DW, Titus-Ernstoff L, McKolanis JR, et al. Conditions associated with antibodies against the tumor-associated antigen MUC1 and their relationship to risk for ovarian cancer. *Cancer Epidemiology, Biomarkers & Prevention*. 2005;14(5):1125-1131.

[71] Jordan SJ, Green AC, Whiteman DC, Webb PM. Australian Ovarian Cancer Study Group. Risk factors for benign, borderline and invasive mucinous ovarian tumors: epidemiological evidence of a neoplastic continuum? *Gynecologic Oncology*. 2007;107(2):223-230.

[72] Gates 2008.

[73] Merritt MA, Green AC, Nagle CM, et al. Talcum powder, chronic pelvic inflammation and NSAIDs in relation to risk of epithelial ovarian cancer. *International Journal of Cancer*. 2008;122(1):170-176 ("Merritt 2008").

[74] Moorman PG, Palmieri RT, Akushevich L, et al. Ovarian cancer risk factors in African-American and white women. *American Journal of Epidemiology*. 2009;170(5):598-606.

[75] Wu AH, Pearce CL, Tseng CC, et al. Markers of inflammation and risk of ovarian cancer in Los Angeles County. *International Journal of Cancer*. 2009;124(6):1409-1415 ("Wu 2009").

[76] Rosenblatt KA, Weiss NS, Cushing-Haugen KL. Genital powder exposure and the risk of epithelial ovarian cancer. *Cancer Causes & Control*. 2011;22(5):737-742 ("Rosenblatt 2011").

Author, Year	Ever/Never Results
Kurta 2012[77]	OR 1.40 (95% CI: 1.16-1.69)
Kotsopoulos 2013[78]	RR 1.19 (95% CI: 0.73-1.96)
Wu 2015[79]	OR 1.46 (95% CI: 1.27-1.69)
Cramer 2016[80]	OR 1.33 (95% CI: 1.16-1.52)
Schildkraut 2016[81]	OR 1.44 (95% CI: 1.11-1.86)

I have identified seven hospital-based case-control studies addressing the association between talc use and ovarian cancer. As set forth in the following table, none of these studies observed a statistically significant association:

Author, Year	Ever/Never Results
Hartge 1983[82]	RR 0.70 (95% CI: 0.40-1.10)
Whittemore 1988[83]	RR 1.45 (95% CI: 0.81-2.60)
Booth 1989[84]	RR 1.30 (95% CI: 0.80-1.90)
Rosenblatt 1992[85]	OR 1.70 (95% CI: 0.70-3.90)
Tzonou 1993[86]	RR 1.05 (95% CI: 0.28-3.98)

[77] Kurta ML, Moysich KB, Weissfeld JL, et al. Use of fertility drugs and risk of ovarian cancer: results from a U.S.-based case-control study. *Cancer Epidemiology, Biomarkers & Prevention*. 2012;21(8):1282-1292.

[78] Kotsopoulos J, Terry KL, Poole EM, et al. Ovarian cancer risk factors by tumor dominance, a surrogate for cell of origin. *International Journal of Cancer*. 2013;133(3):730-739 (study looked at all types of genital powder use at least once a week).

[79] Wu AH, Pearce CL, Tseng CC, Pike MC. African Americans and Hispanics Remain at Lower Risk of Ovarian Cancer Than Non-Hispanic Whites after Considering Nongenetic Risk Factors and Oophorectomy Rates. *Cancer Epidemiology, Biomarkers & Prevention* 2015;24(7):1094-100 ("Wu 2015").

[80] Cramer DW, Vitonis AF, Terry KL, et al. The Association Between Talc Use and Ovarian Cancer: A Retrospective Case-Control Study in Two US States. *Epidemiology*. 2016;27(3):334-346 ("Cramer 2016").

[81] Schildkraut 2016.

[82] Hartge P, Hoover R, Lesher LP, McGowan L. Talc and Ovarian Cancer. *JAMA*. 1983;250(14):1844 ("Hartge 1983").

[83] Whittemore AS, Wu ML, Paffenbarger RS Jr, et al. Personal and environmental characteristics related to epithelial ovarian cancer. II. Exposures to talcum powder, tobacco, alcohol, and coffee. *American Journal of Epidemiology*. 1988;128(6):1228-1240 ("Whittemore 1988").

[84] Booth M, Beral V, Smith P. Risk factors for ovarian cancer: a case-control study. *British Journal of Cancer*. 1989;60(4):592-598 ("Booth 1989").

[85] Rosenblatt KA, Szklo M, Rosenshein NB. Mineral fiber exposure and the development of ovarian cancer. *Gynecologic Oncology*. 1992;45(1):20-25 ("Rosenblatt 1992").

[86] Tzonou A, Polychronopoulou A, Hsieh CC, et al. Hair dyes, analgesics, tranquilizers and perineal talc application as risk factors for ovarian cancer. *International Journal of Cancer*. 1993;55(3):408-410 ("Tzonou 1993").

Author, Year	Ever/Never Results
Hartge & Stewart 1994[87]	RR 0.3 (95% CI: 0.1-1.4) to RR 0.5 (95% CI: 0.2-1.5)[88]
Wong 1999[89]	OR 1.00 (95% CI: 0.80-1.30)

In summary, 11 of the 25 population-based case-control studies do not show a statistically significant association, and none of the hospital-based studies does. Notably, the authors of the case-control studies have generally cautioned, even when they found a statistically significant elevated risk, that their results do not establish causation, either alone or in combination with the results of other studies.[90]

There was also a case-control study of various occupational exposures and ovarian cancer risk published in 2023 that analyzes risk from exposure to cosmetic talc,[91] although it was not a study involving perineal application of talcum powder. The study examined 491 cases and 897 controls and used occupational history linked to a job-exposure matrix to estimate past occupational exposures. Notably, the study was "aimed at generating new hypotheses."[92] Elevated rates of ovarian cancer were found for many professions, including accountants, barbers, beauticians and related workers, sewers and embroiderers, salespeople, shop assistants and demonstrators and in retail trade. Decreased risks were seen for professional nurses. Positive associations were found for 18 varied agents, and strong correlations with each other were noted for many.

The authors did not report a single statistically significant association between occupational cosmetic talc exposure and ovarian cancer. Among ever exposed workers, Leung found a non-significant OR of 1.66 (95% CI 0.80-3.46). The OR dropped among those uncertainly exposed to 0.90 (95% CI 0.69-1.17). When evaluated by duration of exposure (< 8 years and ≥ 8 years) and cumulative exposure (low or high), none of the four reported ORs was

---

87 Hartge P, Stewart P. Occupation and ovarian cancer: a case-control study in the Washington, DC, metropolitan area, 1978-1981. *Journal of Occupational and Environmental Medicine*. 1994;36(8):924-927 ("Hartge & Stewart 1994").

88 *Id.* This study did not provide a value for ever/never use; range reflects values across three strata of use durations.

89 Wong C, Hempling RE, Piver MS, et al. Perineal talc exposure and subsequent epithelial ovarian cancer: a case-control study. *Obstetrics & Gynecology*. 1999;93(3):372-376 ("Wong 1999").

90 *See, e.g.*, Cramer DW, Welch WR, Berkowitz RS, Godleski JJ, Presence of talc in pelvic lymph nodes of a woman with ovarian cancer and long-term genital exposure to cosmetic talc. *Obstetrics & Gynecology*. 2007;110(2 Pt 2):498-501, at 500 (case study stating that "[w]e are not claiming that a causal relationship between ovarian cancer and talc use is proven for this case or in general").

91 Leung L, Lavoué J, Siemiatycki J, Guénel P, Koushik A. "Occupational environment and ovarian cancer risk." *Occupational and Environmental Medicine*. 2023;80(9):489-497.

92 *Id.* at 1.

significant either.[93] In fact, the OR fell when moving from < 8 years of exposure to ≥ 8 years of exposure.

In any event, because the same workers were exposed to so many different exposures of interest, the authors were unable to disentangle whether the identified associations were driven by any given exposure. For example, with regard to hairdressing-related occupations, the authors noted that they were "unable to determine whether the elevated risks observed for agents associated with hairdressing-related occupations were driven by a single agent, a combination of agents, or other workplace factors." Women in these occupations were noted to be exposed to hundreds of chemicals at high concentrations, including hair dyes, shampoos, conditioners, styling and cosmetic products. Formaldehyde was the only one identified by IARC as Group 1. Overall, the authors concluded that "[d]ue to the imprecision of our estimates and the presence of multiple correlated exposures, inferences of these results are limited."

Results of Meta-analyses and Pooled Studies

Meta-analyses and pooled studies, which use statistical methods to pool results from different studies, have also been performed on the body of talc-ovarian cancer epidemiological literature. These studies have calculated overall odds ratios that are generally around 1.3,[94] described in one meta-analysis as a "relatively weak odds ratio[]" that "can be attributed to bias in" case-control studies.[95] As some of these studies have stated, the epidemiological data are "insufficient to establish a causal association between perineal use of talc and ovarian cancer risk" and "not support[ive of] a causal interpretation of the association."[96]

Plaintiffs' experts rely heavily on a 2018 meta-analysis by Penninkilampi and Eslick[97] that "revealed an increased risk of ovarian cancer associated with any perineal use of talc (. . . OR = 1.31; 95% CI = 1.24, 1.39)."[98] The authors of this study state that "the association between talc use and ovarian cancer [has taken] on considerable relevance" because "Johnson & Johnson

---

93 The OR for < 8 years was 1.68 (95% CI 0.72-3.93), ≥ 8 years was 1.51 (95% CI 0.36-6.30), low exposure was 1.34 (95% CI 0.52-3.43), and high exposure was 2.25 (95% CI 0.52-7.41).

94 Berge 2018 at 251 (RR 1.22 (95% CI: 1.13-1.30)); Terry KL, Karageorgi S, Shvetsov YB, et al. Genital Powder Use and Risk of Ovarian Cancer: A Pooled Analysis of 8,525 Cases and 9,859 Controls. *Cancer Prevention Research (Phila)*. 2013; 6(8):811-821 ("Terry 2013") (OR 1.24 (95% CI: 1.15-1.33)); Langseth 2008 (OR 1.40 (95% CI: 1.29-1.52)).

95 Berge 2018 at 253; Cramer DW, Liberman RF, Titus-Ernstoff L, et al. Genital Talc Exposure and Risk of Ovarian Cancer. *Int J Cancer*. 1999; 81(3):351-356, at 354 ("Cramer 1999"); Huncharek M, Geschwind JF, Kupelnick B. Perineal application of cosmetic talc and risk of invasive epithelial ovarian cancer: a meta-analysis of 11,933 subjects from sixteen observational studies. *Anticancer Res.* 2003;23(2C):1955-1960 ("Huncharek 2003") (meta-analysis explaining that "[s]election bias and uncontrolled confounding may account for the positive associations seen in prior epidemiological studies"); Rothman KJ, Pastides H, Samet J. Interpretation of Epidemiologic Studies on Talc and Ovarian Cancer. November 28, 2000; at 4, ("Recall bias can readily introduce enough bias to produce the modestly-sized overall effect (RR = 1.3) that emerges from these studies.").

96 Langseth 2008 at 359; Berge 2018 at 256.

97 Smith-Bindman Am. Rep. at 222, 27, 30, 35; Wolf 2nd Am. Rep. at 9-10, 17-19.; McTiernan 2nd Am. Rep. at 56-58; Siemiatycki 2nd Am. Rep. at 42-43, 87; Cote Rep. at 20-21.

98 Penninkilampi 2018 at 44.

has recently had damages levied to the total of US $717 million against [it] in five law suits" and because "producers of talcum powder products continue to sell these products without any warning labels regarding perineal use and potential associations with ovarian cancer."[99] According to the authors, "there is a need for clarification, to allow women to be adequately informed of the risk of use of these products, possibly preventing future harm."[100] This is an unusual statement in a scientific article and especially odd in an article that is ostensibly premised on the idea that existing science has not concretely defined the risk that the authors are suggesting should be warned against. The study is also puzzling in that its stated purpose is to update prior meta-analyses – in particular, because "the results of a number of large case-control studies and two cohort studies" had been reported since the last meta-analysis was published[101] – and yet, the meta-analysis wholly excluded consideration of the Gates report (the NHS follow-up), another cohort study result published during the same period. Ultimately, notwithstanding the authors' expressed concerns about warning women and updating the research, their conclusions echo those of prior studies, acknowledging in some detail the possibility that recall bias drove the results in the case-control studies[102] and concluding that while the authors believe their results are "suggestive of a causal association," it remains the case that "[a]dditional epidemiologic evidence from prospective studies with attention to effects within ovarian cancer subtype is warranted" and that "it is important that research into this association continue."[103]

Plaintiffs' experts also emphasize a 2019 meta-analysis by Mohamed Kadry Taher and others.[104] This study was funded by Health Canada as part of its assessment of talc and ovarian cancer, which I discuss in the last section of this report. Dr. Smith-Bindman devotes particular attention to the Taher meta-analysis, describing it as a "comprehensive systematic review of the association between any perineal use of talcum powder products and ovarian cancer," stressing its principal finding of a 1.28 OR (95% CI: 1.20-1.37) for any perineal talc use and ovarian cancer and its subgroup findings of 1.39 OR (95% CI: 1.22-1.58) for high frequency of talc use and 1.38 OR (95% CI: 1.22-1.56) for serous ovarian cancer.[105] As with the Penninkilampi study,

---

99 *Id.* at 42.

100 *Id.* at 42.

101 *Id.*

102 *Id.* at 47

103 *Id.* at 47-48. This acknowledgment deserves emphasis in light of the particular weight that plaintiffs' expert Dr. Wolf places on the Penninkilampi study. Dr. Wolf writes that the "Penninkilampi meta-analysis was identified as one of the 'best articles' of 2018 on ovarian cancer" in a recent article by Jason Wright and asserts that the Penninkilampi study "reached th[e] same conclusion" she has – i.e., that "talcum powder can cause ovarian cancer." Wolf 2nd Am. Rep. at 9, 19. But as the language from the Penninkilampi study quoted above indicates, the article actually disclaims a causal conclusion, a fact recognized by the Wright article that Dr. Wolf cites, which states that the "Bottom Line" of the Penninkilampi study is that "[p]erineal application of talc is associated with a small increased risk of ovarian cancer," with no suggestion of a causal conclusion. Wright, JD. What Is New in Ovarian Cancer? Best Articles From the Past Year. Obstet Gynecol. 2018; 132(6):1498-1499, 1499.

104 Taher 2019.

105 Smith-Bindman 2nd Am. Rep. at 21-22. Drs. McTiernan and Cote echo Dr. Smith-Bindman in their reports, which each contain a fairly large discussion of the Taher findings. *See* McTiernan 2nd Am. Rep. at 55-56; Cote Rep. at 20; Drs. Harlow and Rothman and Moorman spend little time analyzing this study other than reporting a few findings. *See* Harlow & Rothman Rep. at 13-14; Moorman Supp. Rep. at 5-6. Drs. Wolf and Siemiatycki also cite to

the justification for the new meta-analysis undertaken by Taher et al. is questionable. The authors cite "increasing concern that perineal exposure to talc, a commonly used personal care product, might be associated with an increased risk of ovarian cancer."[106] Further, they note that "the data describing this association is somewhat inconsistent."[107] But it is not clear why another meta-analysis of the same underlying data would be expected to solve past inconsistency. And indeed, their meta-analysis did not do so. Instead, they reaffirmed the effect of study design on results, with, once again, positive findings only in population-based case-control studies, but not in those with hospital-based controls [0.96 (0.78-1.17)] or in cohort studies [1.06 (0.9-1.25)]. They also highlighted previously demonstrated paradoxical findings, such as lower risk of cancer with longer use of talc and the "expected, yet non-significant, negative association" with talc applied to diaphragms.[108] While they noted a protective effect of tubal ligation [0.64 (0.45-0.92)], they acknowledged incoherent findings of no significant effect of hysterectomy [0.89 (0.54-1.46)] and a small, non-significant higher risk in women with both tubal ligation and hysterectomy [1.06 (0.78-1.42)].[109] Taher et al. also highlighted important limitations on their work, including a section entitled "Applying GRADE framework,"[110] which cautions that the authors "deemed the[ir] findings to be subject to an appreciable risk of bias, mainly due to the potential for recall bias in the included case control studies and relatively short follow-up periods between exposure and outcome assessment in the included cohort studies" and that the limitations of the study designs means that "the certainty of the evidence [reviewed by the authors] was classified as very low."[111] As the authors go on to acknowledge in a footnote, this "very low" classification means that there can be "very little confidence in the effect estimate" and that the "true effect is likely to be substantially different from the estimate of effect."[112] In the conclusion, the authors state that their evaluation is consistent with that of IARC in 2010 and that it "indicates that perineal exposure to talc powder is a possible cause of ovarian cancer in humans."[113] Thus, Taher does not add anything new to the body of literature that preceded it.

A more recent contribution to the body of epidemiologic literature regarding the proposed association between talc use and ovarian cancer is a pooled analysis by O'Brien and others of all

---

Taher et al.'s conclusions, though their reliance is limited to the odds ratios reported for any perineal talc use and ovarian cancer. *See* Siemitaycki 2nd Am. Rep. at 44, 87; Wolf 2nd Am. Rep. at 10.

106 Taher 2019 at 88.

107 *Id.*

108 *Id.* at 95.

109 *Id.* at 96. The authors also note subgroup differences they observed by ethnicity, menopausal state and tubal ligation. But they go on to note that these three subgroup analyses (ethnicity, menopausal state and pelvic surgery) showed considerable heterogeneity that "might have had an impact on the results." *Id.* at 94.

110 *Id.* at 98 & 98 tbl. 4. As described in a reference to a handbook on the GRADE framework contained in the published Taher review, "[t]he GRADE approach is a system for rating the quality of a body of evidence in systematic reviews and other evidence syntheses, such as health technology assessments, and guidelines and grading recommendations in health care." Schünemann H, Brożek J, Guyatt G, Oxman A. GRADE Handbook. (updated Oct. 2013) https://gdt.gradepro.org/app/handbook/handbook.html (cited in Taher 2019 at 98 n.77).

111 Taher 2019 at 98-99.

112 *Id.* at 98 tbl. 4 n.a.

113 *Id.* at 99.

the available cohort study data. This study, published in JAMA, included more than 250,000 women from the Nurses' Health Study, Nurses' Health Study II, Sister Study and Women's Health Initiative, and longer follow-up data for the previously published studies.[114] Specifically, the authors extended follow-up periods to a median of 33.2 years for the Nurses' Health Study, 9.6 years for the Sister Study and 17.4 years for the Women's Health Initiative. The hazard ratio for ever use vs never use of powder was 1.08 [95% CI, 0.99-1.17].[115] The authors found no statistically significant association between use of powder in the genital area and incident ovarian cancer and "no clear dose-response trends for duration and frequency of powder use in the genital area in relation to ovarian cancer risk."[116] Although the study found a weak association when restricted to women with patent reproductive tracts (1.13 [95% CI, 1.01-1.26]), the authors noted that "because the association was not significantly different from that observed in women with nonpatent reproductive tracts, this finding should be considered only exploratory and hypothesis generating."[117] An accompanying editorial noted that the O'Brien study was the largest cohort to date to examine whether an association exists between powder use in the genital area and ovarian cancer risk and that "the findings were overall reassuring."[118]

Plaintiffs' experts emphasize that there are limitations to the O'Brien study, relying heavily on letters to the editor written by other plaintiffs' experts in response to the study.[119] Dr. Smith-Bindman believes that the "primary limitation of O'Brien et al. is the focus on any talcum powder use (a non-specific exposure that combines women across a very broad range of exposures)."[120] This is apparently a reference to the fact that the cohort studies took different approaches to asking participants about frequency and duration of use.[121] Concerns over the adequacy of exposure data were echoed by other plaintiffs' experts too.[122] Differences in ascertainment of exposure appear throughout the literature, however, and are not unique to the cohort studies or the O'Brien pooled analysis. Moreover, as I explain later in this report, exposure is inherently difficult to measure in the context of cosmetic talcum powder application and is a common weakness in all of the studies, whether pooled or not.

Plaintiffs' experts also opine that the O'Brien study might lack sufficient power to identify a slight increase in risk.[123] But the study addressed hundreds of thousands of women,

---

114 O'Brien KM, Tworoger SS, Harris Hr, et al. "Association of Powder Use in the Genital Area with Risk of Ovarian Cancer." *JAMA*. 56. 2020;232(1):49-59 ("O'Brien 2020").

115 *Id.* at 52, Tbl. 1.

116 *Id.* at 56.

117 *Id.*

118 Gossett DR, del Carmen MG. "Use of Powder in the Genital Area and Ovarian Cancer Risk." JAMA. 2020;232(1):29-31, at 30 ("Gossett 2020").

119 Smith-Bindman 2nd Am. Rep. at 29; Plunkett 2nd Am. Rep. at 54; Cote Rep. at 18-19.

120 Smith-Bindman 2nd Am. Rep. at 29.

121 O'Brien at 50.

122 See, e.g. Moorman Supp. Rep. at 5; Singh Supp. Rep. at 11; McTiernan 2nd Am. Rep. at 64, 67-68.

123 See, e.g., McTiernan 2nd Am. Rep. 67.

making it the "largest study of this topic to date."[124] Because of the study's size, the editorial accompanying the O'Brien article concluded that its findings were "overall reassuring."[125]

Several of plaintiffs' experts single out sub-group findings related to patency[126] and highlight statements by Dr. O'Brien that the findings from this sub-group are consistent with a possible association between talc use and ovarian cancer.[127] However, ***after*** this reply by Dr. O'Brien, Dr. O'Brien co-authored a review article the following year that concluded that, even if there were some association that escaped detection in the cohort studies, it would be sufficiently small that, when considered in combination with the lack of other data, it "is difficult to conclude that the observed associations are causal," and the "case for public health relevance is limited."[128] Dr. McTiernan also suggests that the O'Brien analysis did report an 8% increased incidence of ovarian cancer in talc users and maintain that the fact that the finding was not statistically significant does not negate this positive finding.[129] But an 8 percent increase is virtually identical to a null association. Outside litigation, it is hard to imagine such a weak finding being described as meaningful. This is doubly true because, as I discuss later in this report, plaintiffs' experts' frequent disregard of statistical significance is contrary to the approach taken by the scientific community and lacks scientific support.

In 2021, Tanha[130] reported results of an umbrella review of systematic reviews and meta-analyses examining 216 potential risk or protective factors for ovarian cancer, including talcum powder. In their review, they identified four studies that are mentioned above [Penninkilampi 2018; Berge 2016; Huncharek 2003; and Taher 2019]. However, they calculated a combined odds ratio [OR 1.297; 95% CI 1.242-1.355] from just two of these studies. As the primary studies were the same as those involved in the previous meta-analyses, this study just provides a redundant examination of past findings. The Tanha study does not contribute anything meaningful to the subject of perineal talc use and development of ovarian cancer. In addition, the authors stressed that "[t]he ovarian carcinogenesis mechanism of perineal talc use has remained unclear."[131] Overall, the authors noted that among the hundreds of various "protective and risk factors" analyzed, "nutritional and genetic factors play a more profound role," which are categories that did not include perineal talc use.[132] Among the nutritional factors, the authors claim to have identified risk factors for ovarian cancer such as coffee consumption and eating

---

124 O'Brien at 56.

125 Gossett DR, del Carmen MG. "Use of Powder in the Genital Area and Ovarian Cancer Risk." *JAMA*. 2020;232(1):29-31, at 30 ("Gossett 2020")

126 McTiernan 2nd Am. Rep. at 66-67; Siemiatycki 2nd Am. Rep. at 39; Wolf 2nd Am. Rep. at 9; Cote Rep. at 18.

127 Moorman Supp. Rep. at 15; Cote Rep. at 19.

128 Wentzensen 2021, at 9.

129 See, e.g., McTiernan 2nd Am. Rep. 9, 66.

130 Tanha K, Mottaghi A, Nojomi M, et al. "Investigation on Factors Associated with Ovarian Cancer: An Umbrella Review of Systematic Review and Meta-Analyses." *Journal of Ovarian Research*. 2021;14(1):153. Published 2021 Nov 11.

131 *Id.* at 15.

132 *Id.*

eggs, which have clearly not been considered as risk factors by entities, such as CDC, ACOG and NCI.

In 2023, Lynch and colleagues published findings from their systematic review of the association between talc and female reproductive tract cancers.[133] The methodologies for the review used the PRISMA guidelines and incorporated aspects from the IOM and EPA. The search netted 36 studies in humans and 4 in animals. The authors emphasized the importance of considering biologic plausibility and study quality. With regard to animal studies, the authors found ***no evidence*** that talc causes ovarian or other reproductive tumors in rodents after perineal exposure. Cohort studies were found to provide higher quality evidence overall compared to the case-control studies. They noted that overall the better quality studies tended to be negative and the several case-control studies that reported statistically significant associations were all overshadowed by recall and reporting bias. Using the IOM framework, the authors concluded that there is "*suggestive evidence of no association*" between perineal application of talcum powders and risk of ovarian cancer.[134]

Dr. Smith-Bindman has now conducted three meta-analyses (two in prior expert reports and the third in a published paper) addressing talc and ovarian cancer, each of which sought to segment a subset of the data in an apparent effort to identify a higher risk ratio.[135]

In her initial report, Dr. Smith-Bindman purported to conduct a meta-analysis examining whether "regular" talc use causes ovarian cancer because a "narrow[er]" meta-analysis would offer the "most meaningful and consistent results."[136] But Dr. Smith-Bindman never cited any authority in support of this "less is more" theory. The information that she claimed to use for her "regular" use meta-analysis is a subset of information (e.g., frequency of use) that has already been evaluated with regard to dose-response in published meta-analyses, and as I point out elsewhere, the dose-response data, when considered in totality, are highly inconsistent. In this initial litigation meta-analysis, Dr. Smith-Bindman arbitrarily chose to define "regular" talc use as data reporting on at least three talc applications per week, which resulted in an analysis of ten studies.[137] This initial report also contained a second mini meta-analysis that only examined serous invasive data from four studies, a subset of her "frequent" use meta-analysis.[138] This serous invasive analysis was removed from Dr. Smith-Bindman's 2021 amended report, and in her latest report, Dr. Smith-Bindman removed all previous litigation meta-analyses she conducted.

---

133 Lynch HN, Lauer DJ, Leleck OM, et al. "Systematic review of the association between talc and female reproductive tract cancers." *Frontiers in Toxicology*. 2023;5:1157761. Published 2023 Aug 7.

134 The IOM framework has a hierarchical rating scheme of Sufficient evidence of a causal relationship; Sufficient evidence of an association; Limited/Suggestive evidence of an association; Inadequate/Insufficient evidence to determine whether an association does or does not exist; Limited/Suggestive evidence of no association.

135 *See* Smith-Bindman Rep. at 31-34; Smith-Bindman Am. Rep. at 34-37; Woolen et al. (2022).

136 Smith-Bindman Rep. at 30.

137 *See* Smith-Bindman Am. Rep. at 35.

138 *See* Smith-Bindman Rep. at 32, 34.

After issuing her report in this litigation, Dr. Smith-Bindman provided her litigation meta-analysis on "frequent" use to a colleague, Dr. Sean Woolen, who utilized her report (with some modifications) to generate a peer-reviewed publication that contained nearly identical results.[139] Notwithstanding the fact that this study was based on prior litigation work, the study protocol for what came to be Woolen 2022 was "prospectively registered" in PROSPERO in 2020 where the authors misleadingly reported that data extraction and data analysis had not started. This is expressly contradicted by testimony from Dr. Smith-Bindman in 2019 where she stated with respect to this forthcoming publication that "the analysis that I have done is complete"[140] In addition, co-author Dr. Woolen already knew about Dr. Smith-Bindman's earlier analysis and findings because Dr. Smith-Bindman stated she had already "sent him [her] report."[141] Notably, Woolen 2022 extracted and analyzed data from 11 studies, nine of which had already been included in the earlier litigation analysis.[142] In the Woolen article, the work is represented as a hypothesis testing exercise ("we hypothesize that . . ."), which would lead a reader to believe that the authors were newly testing a hypothesis, even though the answer to the study question was already largely known to the authors at the time of the updated analysis.

Of note, Dr. Woolen was aware of the bias they were bringing to the paper. He emailed Dr. Smith-Bindman, stating "I removed all content from the litigation and news media because I think we will get called out from [sic] our litigation bias."[143] It is unclear what, if anything, the authors did to address their litigation bias other than remove references that would highlight it. While Dr. Smith-Bindman discloses she works for plaintiffs in talc litigation, there is no particular statement apprising colleagues that *this* paper arose from litigation. The authors' decision to withhold this fact is extremely concerning.

The updated analysis in Woolen 2022 had some modifications as compared to Dr. Smith-Bindman's previous "frequent" talc use meta-analysis drafted for litigation. Without explanation, the definition of "frequent" talc use was reduced from >=3 times per week to >=2 times per week. In addition, unpublished data were now included, and there was now a quality assessment applied to the included articles. The updated study produced a summary OR of 1.47, nearly identical to the previous 1.43 produced from the litigation effort. Once again, the meta-analysis performed by Dr. Smith-Bindman examined only a subset of data from a truncated number of the epidemiologic studies, using a methodology that systematically excluded the majority of data from the cohort studies.

With regard to the use of the Newcastle-Ottawa Scale (a tool to assess study quality), it is notable that Woolen et. al. found all of the studies to grade in the range of 7-9, reflecting a high-

---

139 Woolen SA, Lazar AA, Smith-Bindman R. "Association Between the Frequent Use of Perineal Talcum Powder Products and Ovarian Cancer: a Systematic Review and Meta-analysis." *Journal of General Internal Medicine*. 2022;37(10):2526-2532.

140 Smith-Bindman Dep. Vol. II, 356: 16-21.

141 Smith-Bindman Dep. 2021, 36-37: 1-2.

142 The only distinctions in terms of studies included/excluded are that (1) Dr. Smith-Bindman had erroneously omitted Rosenblatt 2011 from her litigation meta-analysis (a study that reduced her overall OR) and (2) Woolen 2022 added partial data from a single cohort study, NHS-1.

143 Smith-Bindman Dep. 2021, 84: 9-13.

quality study with low risk of bias. Taher and colleagues (cited in Woolen), found two of those same studies to reflect a high risk of bias [Mills 2004 and Whittemore 1988]. Overall, 7 of 9 studies were graded more favorably by Woolen than Taher. (The validity of Dr. Smith-Bindman's quality assessment may have been affected by her inexperience in grading studies. Q: Do I understand that you had never used the Newcastle-Ottawa Scale previously A: That's correct. I had never used a quantitative scale which assigns points for each of those features before."[144] It is also odd that in the Woolen paper, the Rosenblatt study was graded 8 of 9, even though Dr. Smith-Bindman had previously testified that she "did not think it was a high quality study."[145] Furthermore, Taher and colleagues appropriately evaluated the studies with the GRADE framework to assess the quality of evidence from the underlying studies (which was not done by Woolen), and found them to be "subject to an appreciable risk of bias." Taher initially concluded the certainty of evidence derived from observational studies was "low" but later "downgraded" the level "to very low certainty in light of the risk of bias." Woolen et. al. (though citing Taher) notably downplayed the risk of bias, contending that it is only an issue for the Schildkraut study. The risk of bias is not even listed in the section of study limitations.

There are a number of other limitations/concerns with respect to this paper. The first is investigator bias in the handling of the unpublished data from O'Brien. The authors noted in a footnote to Table 2 that while they were provided "the entirety of data" from O'Brien, they chose to only include data on women with intact fallopian tubes. The stated reason was "to harmonize with other publications." ("I remember raising the question, and Sean decided to use it for women with openly productive tracts. [sic] And his argument was that many of the studies we have read only included women with open reproductive tracts, so that definition would be most consistent with and harmonious with the other studies that we included."[146]) This justification is not consistent with the rest of the paper. The Woolen study description did not have any inclusion criterion related to patency of the reproductive tract. Instead, this selectively applied criterion allowed Woolen to only use the one subgroup analysis in O'Brien that did not report null results. In short, while systematically excluding nearly all data from cohort studies (knowing that they had null results), Woolen chose only a subset of unpublished data from a single cohort study, that the authors already knew had shown a small statistically significant association (*see* Woolen discussion p. 2531).

None of the other 10 studies included in the Woolen study restricted study subjects to those with a patent reproductive tract. Some, but not all, of the studies analyzed the effect of tubal ligation and/or hysterectomy on the relationship between talcum powder exposure and risk of ovarian cancer. Findings were mixed when tubal ligation and hysterectomy were considered with some showing modification of measured risk and some not. For example, in Mills 2004, the risk was lower if there had been a tubal ligation, though the interaction term was not significant.

144 Smith-Bindman Dep. 2021, 76: 3-5, 21-23.

145 Smith-Bindman Dep. 2021, 100: 15-17.

146 Smith-Bindman Dep. 2021, 59:13-19.

In that study, there was no effect of hysterectomy.[147] In Booth 1989, risk was decreased.[148] In Rosenblatt 2011, risk was slightly decreased if fallopian tubes were intact.[149] In Harlow 1992, there was no impact on the results if subjects were excluded with talc exposure after tubal ligation or hysterectomy.[150] It therefore cannot be said that restricting the unpublished O'Brien data to those with a patent reproductive tract achieved harmonization with the other studies; it achieved the exact opposite. The choice to restrict the O'Brien data thus raises concern that the purpose was to skew the overall study findings in a positive direction. Notably, the authors showed the overall effect of narrowing their analysis to women with patent fallopian tubes in a supplemental table. The unpublished data showed an adjusted HR of 1.40 in women with patent fallopian tubes, but the HR was only 1.27 if all women had been considered.

Another concern is the authors' statement that their study is the first to focus on frequent use of talc. While their statement of "focus" may be true, it is misleading to suggest that they are the first to examine the issue. As noted above, multiple previous studies had already considered frequency and duration of talc use, with inconsistent findings when viewing the entirety of available data. The lack of novelty is apparent when Dr. Smith-Bindman discussed the earlier litigation versions of the analyses: "My systematic review ended up with the same estimates as essentially all of the other well-done systematic reviews . . . .the results of my meta-analysis and the previous ones are nearly identical. So, yes, it was a very close replication."[151]

When asked about her selected measure of "regular" talc use in her litigation meta-analysis, Dr. Smith-Bindman admitted it was "subjective."[152] This is an understatement and applies with equal force to Woolen 2022. In her litigation meta-analysis, she originally defined "regular use" as "at least 3x per week, or where the total number of lifetime applications corresponded to approximately daily exposure."[153] In Woolen 2022, the authors changed the definition of "frequent" to at least 2x per week without any explanation. Far too many questions arise from these vague and subjective criteria. For example, why did Dr. Smith-Bindman arbitrarily choose two uses per week as the lower threshold for regular use? Notably, this cut-off precisely excludes all the published data in O'Brien 2020, which reported on women who used talc more than *once* per week. Indeed, O'Brien 2020 defined "frequent" as such, and the Woolen paper offers no explanation as to why they deviated from this previous definition of "frequent" use. The most logical explanation is that the authors sought to exclude as much data from the

---

147 Mills PK, Riordan DG, Cress RD, Young HA. Perineal talc exposure and epithelial ovarian cancer risk in the Central Valley of California. *International Journal of Cancer*. 2004;112(3):458-464.

148 Booth M, Beral V, Smith P. Risk factors for ovarian cancer: a case-control study. *British Journal of Cancer*. 1989;60(4):592-598.

149 Rosenblatt KA, Weiss NS, Cushing-Haugen KL. Genital powder exposure and the risk of epithelial ovarian cancer. *Cancer Causes & Control*. 2011;22(5):737-742.

150 Harlow BL, Cramer DW, Bell DA, Welch WR. Perineal exposure to talc and ovarian cancer risk. *Obstetrics & Gynecology*. 1992;80(1):19-26.

151 Smith-Bindman Dep. Vol. II, p. 355: 12-14; 356:7-8.

152 Smith-Bindman Am. Rep. at 37 ("I tried to be consistent in defining exposure, but this factor was subjectively determined by the individual studies."); *see* Smith-Bindman Dep. Vol. II 272:3-273:3 (Smith-Bindman "tried to approximate regular use" and has not validated her metric).

153 Smith-Bindman Am. Rep. at 35.

cohort studies as possible. What is even more concerning is that none of the data actually included in the Woolen paper equates to two or even three uses per week. The data actually used in the study correspond to a minimum of 4x use per week.[154] It is inaccurate to claim they are reporting on "frequent" use of at least 2x per week when the actual usage frequency is far higher. The seemingly arbitrary decision to equate "regular" talc use with at least 2x use per week raises serious methodological concerns. And importantly, whether a study reported on "regular" talc use appears to be the sole criterion the authors employed in choosing studies for this review.

The authors' statement that asbestiform talc is considered by IARC to be a class 1 carcinogen is also of concern. That statement is a misleading reference to what IARC states at the cited reference to "Talc containing asbestiform fibres (see Asbestos)." That same reference clearly states the grade is 2B (possibly carcinogenic) for "Talc-based body powder (perineal use of)." It is highly misleading to discuss IARC findings in this paper, without explaining to the reader that the most directly relevant IARC finding that is specific to perineal use of talc-based body powder did not find it to be a "class 1 carcinogen."

I note too that the NCI PDQ references the Woolen paper in a discussion of "Factors with Inadequate Evidence of an Association: Risk of Ovarian, Fallopian Tube and Primary Peritoneal Cancers."[155] The PDQ refers to the paper as "A meta-analysis of ten case-control studies and a highly selected subset analysis of one prospective cohort study . . . ." Further, the authors point out that "the subset analysis of the prospective study was inconsistent with the main findings of the report," and that the "results should be interpreted with care." After considering the Woolen paper along with the body of relevant literature generally, the NCI concluded: "Results from case-control and cohort studies are inconsistent so the data are inadequate to support an association between perineal talc exposure and an increased risk of ovarian cancer." The NCI PDQ communication to health professionals is that the Woolen paper has limitations requiring it to be "interpreted with care" and that it does not change the overall inadequacy of available evidence to show that perineal talc application is a risk factor for ovarian cancer.

Bias

Bias is a significant concern when analyzing whether perineal exposure to talcum powder causes ovarian cancer because, as set forth above, the reported risks are very small, which is often indicative of bias issues rather than a causal association.[156] Notably, before he was retained as an expert for plaintiffs, Dr. Rothman stated that recall bias "can readily give rise to associations of" the magnitude seen in the epidemiological studies on talc use and ovarian cancer.[157]

---

154 Woolen 2022 (Table 2).

155 National Cancer Institute. Ovarian, Fallopian Tube, and Primary Peritoneal Cancer Prevention (PDQ)-Health Professional Version, updated October 16, 2023. https://www.cancer.gov/types/ovarian/hp/ovarian-prevention-pdq.

156 Rothman 2000 at 1; Wynder EL et al. Conference Report: Weak Associations in Epidemiology and Their Interpretation. Prev. Med. 1982;11:464-476, at 465 ("Because chance or bias can easily produce a spurious weak association, the need to seek supporting evidence is greater with weak than with strong associations.").

157 Rothman 2000 at 1.

This is particularly true because the association is only seen in case-control studies, which are particularly susceptible to bias,[158] although hospital-based studies may be less distorted by recall bias than population-based studies because the former feature both ill cases and ill controls.[159] Plaintiffs' experts downplay the impact of recall bias in case-control studies as "minimal"[160] or "theoretical,"[161] but this claim is unsupported, and the scientific literature that has directly addressed the question has shown it to be quite wrong.

One talcum powder study examined the issue of bias directly, and it found striking and clear evidence of the impact of recall bias on the study results. In the case-control study reported by Schildkraut et al., the authors (including plaintiffs' expert Dr. Patricia Moorman) considered that "the possibility of differential misclassification exists in a case-control study such as AACES, especially due to the heightened awareness of the exposure as a result of" well-publicized litigation.[162] The investigators examined their finding based on whether the study subjects were interviewed before 2014 versus 2014 onward. Among those interviewed before 2014, the reported use of body powder on the genitals was nearly the same for cases and controls (36.5 and 34.0%, respectively). But from 2014 onward, the reported use among cases was markedly higher (51.5%), while it stayed the same in controls (34.4%). This striking and abrupt change in reporting clearly demonstrates the major impact of recall bias. It also calls into question earlier results because the question of talc and ovarian cancer did not emerge for the first time in 2014, and earlier studies could well have been affected by a more modest but nonetheless significant recall bias. Clearly, media reporting about talc and ovarian cancer did not begin in 2014; rather, there are multiple news reports between 1982 and 2013 (**See Appendix A: Sample Of Pre-2014 News Articles Addressing Posited Link Between Talc Use And Ovarian Cancer, for a list of examples**). Women with ovarian cancer in that era could easily have been influenced in their recall of talcum powder use, which would potentially amplify recall bias in pre-2014 studies as well. And, in any event, as discussed elsewhere in this report, recall bias is affected by factors other than media reports.

Further evidence for recall bias was found in a 2023 study by O'Brien on reliability of self-reported douching and genital talc.[163] The authors found that while "self-reported talc use" was more commonly reported "on the enrollment questionnaire" relative to the latest follow-up in the full sample, "the trend was reversed among those with intervening ovarian cancer diagnoses."[164] The authors explicitly noted these findings "may indicate recall bias is present and

---

158 Berge 2018 at 253 ("The fact that the association between genital talc use and risk of ovarian cancer is present in case-control, but not in cohort studies, can be attributed to bias in the former type of studies.").

159 Infante-Rivard C. Hospital or Population Controls for Case-Control Studies of Severe Childhood Diseases? *American Journal of Epidemiology*. 2003;157(2):176-182.

160 Wolf 2nd Am. Rep. at 10.

161 McTiernan 2nd Am. Rep. at 23, 28; *see also* Harlow & Rothman Rep. at 6 ("recall bias typically has a negligible effect, and in our opinion, it is not plausible that recall bias can explain away the association").

162 Schildkraut 2016 at 1416.

163 O'Brien KM, Ogunsina K, Wentzensen N, Sandler DP. "Douching and Genital Talc Use: Patterns of Use and Reliability of Self-reported Exposure." *Epidemiology*. 2023;34(3):376-384.

164 O'Brien 2023 at 383.

potentially driving some of the previously observed differences in effect estimates" between case-control and cohort studies.[165]

Other study authors have recognized the problem of bias in their studies as well. For example, a 2017 pooled study of 12 case-control studies addressing ovarian cancer risk factors in four ethnic groups found a statistically significant elevated risk for talc use among two of the four ethnic groups (Non-Hispanic White (OR 1.30 (95% CI: 1.20–1.41)) and Black (OR 1.62 (95% CI: 1.32–2.00)) and no statistically significant elevated risk for the other two groups (Hispanic (OR 1.41 (95% CI: 0.93–2.13)) and Asian/Pacific Islander (OR 1.02 (95% CI: 0.61–1.70))).[166] The authors characterized the differences across groups as "[s]tudy heterogeneity" and cautioned: "A concern with self-reported data is recall bias, especially for characteristics that are difficult to report with accuracy, require subjective summarization or can be influenced by the investigator, media or similar factors. Such problematic characteristics may include body powder exposure[.]"[167]

Goodman and colleagues[168] conducted a study to better understand the potential impact of recall bias on the results of case-control studies of perineal talc use and ovarian cancer. They examined data from Cramer 2016 and applied sensitivity and specificity estimates for recall by study subjects who were cases and controls. Applying the sensitivities and specificities derived from O'Brien 2020, the bias-adjusted OR reversed direction from the original weakly positive OR. Where the estimate was OR 1.30 (95% CI 1.13-1.48), with adjustment for bias, it was OR 0.62 (95% CI 0.36-0.95). Using lesser degrees of bias than estimated from O'Brien, the ORs were attenuated and not significantly different from the null. The authors concluded that recall bias alone may have a large effect on risk estimates, and that because other studies used similar methods to estimate exposures, it is likely that bias affected other case-control studies as well.

Confounding

Similarly, confounding factors may have affected the results of studies that found a small estimated risk pertaining to perineal exposure to talcum powder and ovarian cancer. This issue is especially concerning when it comes to ovarian cancer risk because, generally, scientists do not know the cause of ovarian cancer. Thus, even studies that attempt to account for known confounders (such as familial or genetic risk) likely do not account for most of the risks – known or unknown.

The Sister Study[169] provides insight into one potential source of confounding in prior studies. In that study, the investigators accounted for douching, an exposure not considered in nearly all of the other studies. The authors were interested in douching because of concerns that

---

165 *Id.*

166 Peres LC, Risch H, Terry KL, et al. Racial/ethnic differences in the epidemiology of ovarian cancer: a pooled analysis of 12 case-control studies. *International Journal of Epidemiology*. 2018;47(2):460-472.

167 *Id.* at 8-9.

168 Goodman JE, Espira LM, Zu K, et al. Quantitative recall bias analysis of the talc and ovarian cancer association. *Global Epidemiology*. 2024;7:1-4.

169 Gonzalez 2016.

it could "introduce particles and toxicants in the upper reproductive tract and increase the risk of cancers and infections." They cited evidence that douching products contain phthalates that "could influence ovarian cancer risk through hormone disruption." The study found that douching was a risk factor for ovarian cancer (HR 1.8 (1.2-2.8)), while talc use was not (HR 0.73 (0.44-1.2)). Douching, with or without concurrent talc use, had similar risk (HR 1.8 and 1.9, respectively). The investigators noted that the practice of douching and talc use are correlated and that "if douching is a risk factor for ovarian cancer, some of the earlier reports on talc could have been subject to confounding bias." The same study also showed that douche users are different from non-users, with users more likely being Non-Hispanic Black, of lower educational attainment and/or obese. These systematic differences highlight the complexity of understanding the potential effect of a non-random feminine hygiene practice and judging causation when estimated risks are otherwise so small.[170]

The finding in Gonzalez that the douche users had lower educational attainment suggests that socioeconomic status may be another important confounder. Indeed, in another study by Alberg et al., the investigators found that higher educational attainment may be protective against developing ovarian cancer (or in other words, low educational attainment is associated with higher risk of developing ovarian cancer).[171] The authors noted that if socioeconomic status is truly protective, the reasons for the relationship still need to be identified.[172] They suggested that differences in diet and exercise could be related to risk, which overall means that assessing confounding in ovarian cancer studies is important, complex and not yet fully developed in research.[173] What is important in assessing the epidemiologic studies of talc and ovarian cancer is that, as plaintiffs' experts have acknowledged, the studies did not use a uniform approach to assessing confounders, with, for example, nearly all not adjusting for douching and many not accounting for education or socioeconomic status.[174] Accordingly, any argument that confounding is unlikely because studies have reported small differences between adjusted and

---

[170] A case-control study by Iwona M. Gabriel and others, including Daniel W. Cramer, a plaintiffs' expert in prior talc litigation, and two other co-authors disclosing employment as plaintiffs' experts in talc litigation, also addresses douching and talc use. It reports odds ratios for epithelial ovarian cancer and various exposure histories relative to women who never used talc and did not douche regularly, including the following: 0.94 (95% CI: 0.76-1.16) for women who regularly douched but never used talc; 1.28 (95% CI: 1.09-1.51) for women who ever used talc but did not douche regularly; 0.83 (95% CI: 0.52-1.33) for women who both ever used talc and used homemade douches regularly; and 1.53 (95% CI: 1.11-2.10) for women who both ever used talc and used store-bought douches regularly. These conflicting data concerning the possible associations among talc use, douching and types of douching products used raise more questions than they answer and highlight the difficulties in drawing conclusions from the case-control studies. Gabriel IM, Vitonis AF, Welch WR, et al. Douching, talc use, and risk for ovarian cancer and conditions related to genital tract inflammation. *Cancer Epidemiology, Biomarkers & Prevention*. 2019;28:1835-1844.

[171] Alberg AJ, Moorman PG, Crankshaw S, et al. Socioeconomic Status in Relation to the Risk of Ovarian Cancer in African-American Women: A Population-Based Case-Control Study. *American Journal of Epidemiology*. 2016;184(4):274-283.

[172] *Id.* at 282.

[173] *Id.*

[174] Smith-Bindman Dep. Vol. II 307:21 -308:24; Moorman Supp. Rep. at 3 ("[M]ost of the papers describing the association between talc use and ovarian cancer have not examined douching as a potential confounding variable."); Siemiatycki 2nd Am. Rep. at 65 (noting that there is "variability between studies in the list of covariates" and failing to mention any adjustment for douching or socioeconomic factors).

crude results is overly simplistic (and in any event ignores that studies cannot adjust for unknown confounders).

In the most recent evaluation of cohort studies of perineal talc use and ovarian cancer,[175] the authors discussed the study limitations that include potential confounding. The authors noted the potential for residual confounding, which would occur if the studies to date have not sufficiently accounted for potential confounders. They also raised the possibility of confounding by indication, which would occur if women with other conditions associated with ovarian cancer are also more likely to use powder in the genital area. As noted by Wentzensen and O'Brien, "an example relevant to the powder-ovarian cancer association is if a hormone-related condition was a risk factor for ovarian cancer, and also altered the vaginal environment in a way that made women more or less likely to apply genital powder."[176] In that situation, it would be the hormone-related condition, not the talc use, that would be the risk factor for ovarian cancer.

A very recent, 2024 paper, based on the Sister Study cohort,[177] examined the potential association between various personal care product (PCP) mixtures and female cancers (breast, ovarian, uterine). The authors noted that "few epidemiologic studies have investigated the contribution of PCP use to the risk of women's hormone-sensitive cancers," and that "existing research has largely focused on only certain products such as hair dyes, hair straighteners/relaxers, deodorant, genital talc, and douching products," citing Gonzalez 2016 and Penninkilampi 2018, among others.[178] The authors further stated that "previous studies predominantly assessed the effect of individual products separately" and expressed concern that "[t]aking a single product approach is limiting because it fails to account for potential confounding by concurrently used products and does not reflect the risk associated with multiple products simultaneously in real-life settings."[179] Recognizing the limitations of the prior research, the authors aimed to examine the associations between use of everyday PCPs and cancers, including ovarian, with a focus on the joint effects of multiple product use.

The study examined the frequency of use of 41 PCPs, which were analyzed separately, as well as by groups (beauty products, hair products, hygiene products and skincare products). Genital talc was one of the eight hygiene products studied, along with bath/shower gel, deodorant/antiperspirant, douche, mouthwash/rinse, shaving cream, talc (under arm), and talc (other areas). The authors reported positive associations for ovarian cancer with the beauty product mixture [HR=1.08; 95% CI (0.85, 1.37)] and hygiene product mixture [HR=1.35; 95% CI (1.00, 1.83)], "with douche being the most important component" in the hygiene mixture.[180] In fact, within the hygiene category, the ***only*** single product found to be significantly associated

---

175 O'Brien 2020.

176 Wentzensen N, O'Brien KM. "Talc, Body Powder, and Ovarian Cancer: A Summary of the Epidemiologic Evidence. *Gynecologic Oncology*. 2021;163(1):199-208 at 5.

177 Chang CJ, O'Brien KM, Keil AP, et al. "Use of personal care product mixtures and incident hormone-sensitive cancers in the Sister Study: A U.S.-wide prospective cohort." Environmental International. 2024;183:1-16.

178 *Id.* at 2.

179 *Id.*

180 *Id.* at 4.

with ovarian cancer was douche [HR=1.31; 95% CI (1.06, 1.63)].[181] In contrast, the authors reported a non-significant HR of 1.04; 95% CI (0.91, 1.19) for vaginal talc use, which was slightly less than under arm talc use [HR=1.05; 95% CI (0.93, 1.13)] and right in line with the association for bath gel use [HR=1.04; 95% CI (0.96, 1.13)].[182] This study suggests that if there is an increased risk of ovarian cancer from PCPs, it does not appear to relate to genital talc, but rather to douching.

The study also demonstrates that adjusting for confounding effects of other personal care products is essential to the study of individual product types (such as genital talc), without which the incorrect conclusion will be reached. Interesting findings were presented for ovarian cancer risk and use of beauty products, which appears stronger in Black than in non-Hispanic White women. The authors highlighted that this finding may be explained by more frequent use of certain products in Black women that were the primary positive contributors to ovarian cancer incidence. These products were perfume, artificial nails, cuticle cream, and nail polish remover. What this study makes abundantly clear is that the relationship and interrelationship of personal care products used by women is extremely complex and that an ovarian cancer cause, if there is one, cannot be explained by a single product type.

Other Concerns Regarding Plaintiffs' Experts' Analysis Of Strength

Some of plaintiffs' experts have provided confusing opinions about strength of association. While the strength of association between talcum powder use and ovarian cancer is indisputably small, these experts have nevertheless found it to be "strong" by discussing their judgments about the potential importance of the findings and also by bringing in other arguments, such as statistical significance. For example, Dr. Smith-Bindman states: "It is frequently argued that the larger an apparent association, the more likely the association is to be real (causal) and important for epidemiological assessment. This would suggest that an OR of 2.0 is more likely to indicate causality and importance than an OR of 1.5. While this is often argued, this is untrue . . . [i]f a risk factor increases the risk of disease by 50%, and the exposure is common, it will have far greater impact on a number of people [], in comparison to a rare exposure that has a higher associated relative risk. Perhaps a larger association between exposure and disease may be easier to identify, but it is no more likely to indicate causality or importance."[183]

While the strength of association between talcum powder use and ovarian cancer is indisputably small, Dr. Smith-Bindman states that "[t]he data supporting the causality of talcum powder products exposure for ovarian cancer is extremely strong."[184] She reaches that conclusion by calculating the number of ovarian cancers she believes are caused by talcum powder products and using this calculated "number of people impacted" to support her statement

---

181 *See id.*

182 *Id.* (Table S4).

183 Smith-Bindman 2nd Am. Rep. at 32.

184 Smith-Bindman 2nd Am. Rep. at 33; *see also* Cote Rep. at 36 (despite noting modest increase of 1.25, "I give strong weight to the strength of association and consistency").

that "[t]he Bradford Hill Factor of the Strength of the association is met."[185] Dr. Wolf likewise asserts that the small point estimates reported in the literature nevertheless support the strength consideration because ovarian cancer is "difficult to diagnose and deadly," making any increase in risk "clinically significant" and "critically important."[186] And Dr. McTiernan states that because "ovarian cancer [is] a life-threatening disease," the small "increased relative risks . . . seen in the epidemiologic studies . . . should not be characterized as 'weak' or 'small.'"[187]

In other words, these experts are contending that because talc use would be responsible for significant numbers of life-threatening diseases if their causal hypotheses were correct, the association is "strong." This statement is misleading and circular because plaintiffs' experts are relying on the "impact" or "importance" of a finding of causation, which is only impactful or important if true, to support the judgment that the very small association is causal. One needs to first determine if an association is causal, and only then, if it is causal, decide on its importance.

Finally, Drs. Smith-Bindman and Wolf also contend that higher odds ratios apply with respect to the particular histologic subtype of serous ovarian cancer.[188] But this alternative approach to the issue of strength does not materially affect the analysis. The odds ratio of 1.4 or 1.5 for invasive serous remains well below 2.0 and would still be considered a weak association. The studies offering odds ratios for serous ovarian cancer, like the broader pool of studies, contain a mix of results, with some reporting statistically significant findings and others not.[189]

* * *

Based on the foregoing, it is my opinion that the association between perineal talcum powder exposure and ovarian cancer is weak and likely impacted by bias, confounding and/or chance. Moreover, plaintiffs' experts' attempts to explain away these problems and cast the science as standing for essentially the opposite proposition – that the epidemiology establishes a strong or conclusive association – strongly suggest that they are engaged in advocacy rather than science.

Epidemiologic Studies Are Inconsistent.

As set forth above, the prospective epidemiologic studies (cohort studies) do not show a statistically significant association, while only a subset of the population-based case-control

---

185 Smith Bindman 2nd Am. Rep. at 33-34.

186 Wolf 2nd Am. Rep. at 18.

187 McTiernan 2nd Rep. at 32.

188 Wolf 2nd Am. Rep. at 17 ("If invasive serous is considered exclusively, the association is even stronger."); Smith-Bindman 2nd Am. Rep. at 33 (performing an analysis on invasive serous cases in an effort to show strength factor is met).

189 A previous version of Dr. Smith-Bindman's report cited four studies on serous ovarian cancer and talc use, one of which (Cook 1997) reported a statistically insignificant result, and two of which have confidence intervals that are barely above 1.0). Smith-Bindman Am. Rep. at 37 fig. 3.

studies does.[190] This disparity reflects inconsistent results across different types of studies, undermining the conclusion that cosmetic talc use causes ovarian cancer. The fact that none of the cohort studies found a statistically significant association between talc use and ovarian cancer is critical in this regard,[191] because it calls into doubt even the modest association in some of the population-based case-control studies.

Other inconsistencies exist in the literature as well, including some that overlap with the concepts of coherence and plausibility.[192] Evaluating an association with the use of talc-dusted diaphragms and condoms has been deemed "the most valid method for testing the carcinogenic potential of talc" because "[b]y definition, the female reproductive tract is exposed to talc containing powders introduced by diaphragms, whereas an exposure route based on perineal dusting requires unproven assumptions about vaginal exposure."[193] Studies pertaining to use of talcum powder on diaphragms and condoms have shown a consistent lack of risk. As noted above, it is illogical that talcum powder applied to the outside of the genital tract can cause ovarian cancer, while talcum powder applied inside the genital tract would not. Additionally, the assertion by plaintiffs' expert Dr. Smith-Bindman that one systematic review of diaphragm studies can be ignored because it was of "poor quality"[194] is unfounded and, in any event, fails to address the underlying studies that show no risk.

Many of plaintiffs' experts take the position that the data on the association between genital talc use and ovarian cancer are highly consistent, but their explanations are not scientific.

For example, Dr. Smith-Bindman states that there has been "relative stability in the estimated increase in the risk of ovarian cancer associated with talc powder products use . . . across time and in diverse populations with diverse study designs."[195] Dr. Plunkett similarly asserts that epidemiological data show "a consistent signal for ovarian cancer in women exposed to talcum powder products."[196] Dr. Cote's analysis of the consistency factor is even more perfunctory and just concludes that "effect sizes seen across populations [are] strikingly consistent."[197] This consistency analysis is faulty.

---

190 As just explained, this disparity holds for the subtype of serous ovarian cancer as well, as to which the Gates study reported no statistically significant association.

191 Berge 2018 at 251.

192 Fiume MM, Boyer I, Bergfeld WF, et al. Safety Assessment of Talc as Used in Cosmetics. *International Journal of Toxicology*. 2015;34(1 Suppl):66S-129S., at 119S ("Fiume 2015"); Hartge 1983; Muscat JE, Huncharek MS. Perineal talc use and ovarian cancer: a critical review. Eur J Cancer Prev. 2008; 17(2):139-146, 144-145 (2008) ("Muscat & Huncharek 2008").

193 Muscat & Huncharek 2008.

194 Smith-Bindman 2nd Am. Rep. at 23.

195 *Id.* at 34.

196 Plunkett 2nd Am. Rep. at 91; *see also* Wolf 2nd Am. Rep. at 18 ("Results are generally consistent across case-control, meta-analysis, and pooled analysis studies.").

197 Wolf 2nd Am. Rep. at 18. Dr. Cote's analysis of the consistency factor is extremely perfunctory and just claims "effect sizes seen across populations [are] strikingly consistent". Cote Rep. at 36. This does not meaningfully

First, these statements omit the fact that while some of the case-control studies have shown a small positive risk, the cohort studies have uniformly failed to demonstrate one.[198] Instead, plaintiffs' experts are forced to ignore the findings of cohort studies by deeming them "not well designed to determine true risk."[199] Along similar lines, Dr. Smith-Bindman states that the cohort studies "did not focus on the details of th[e] topic" of "the relationship between talcum powder products exposure and ovarian cancer" because they were "not sufficiently nuanced to provide meaningful information" due to poor "measurements of exposure" and "short follow-up periods," claimed shortcomings that, in her view, "negate[] an advantage of cohort studies."[200] But these criticisms of cohort studies are misplaced, as previously discussed. In any event, this argument assumes that the results of some studies are not consistent, or else there would be no reason for plaintiffs' experts to find fault with the cohort study designs.

Second, plaintiffs' experts' statements claiming consistency across populations and study designs ignore the very real differences between population-based and hospital-based studies mentioned above. They also ignore the lack of a significant association between use of talc use and epithelial ovarian cancer for African-American women found in Davis 2021.[201]

Plaintiffs' experts also claim that consistency is met notwithstanding the lack of significant findings in both case-control and cohort studies because "the classification of study results into 'significant' and 'non-significant' based on statistical significance and a p-value is often arbitrary and leads to an invalid interpretation of the data."[202] Dr. McTiernan and Dr. Siemiatycki similarly abandon statistical significance, claiming that it is "irrelevant because most individual studies did not have sufficient statistical power" to find such low levels of possible risk.[203] In a similar vein, Dr. McTiernan also claims that the results from Davis 2021 support consistency because findings across different racial groups showed an association,[204] but she again ignores the fact that the results in African-American women were not statistically significant.[205]

---

engage with the differences between population-based and hospital-based studies, nor the differences between case-control and cohort studies.

198 Dr. Smith-Bindman acknowledged in deposition testimony that cohort studies are generally understood this way, although she expressed her disagreement with that view. Smith-Bindman Dep. Vol. I 239:6-240:5.

199 McTiernan 2nd Am. Rep. at 89; *see also* Singh Supp. Rep. at 20.

200 Smith-Bindman 2nd Am. Rep. at 17.

201 Davis 2021 at OF6 (reporting an OR for African-American women of 1.22 (95% CI 0.97-1.53)).

202 Smith-Bindman 2nd Am. Rep. at 16.

203 Siemiatycki 2nd Am. Rep. at 70; McTiernan 2nd Am. Rep. at 89; *see also* Singh Supp. Rep. at 20 ("the findings of a non-statistically significant increased risk in the cohort studies . . . should not be deemed inconsistent" with the other findings).

204 McTiernan 2nd Am. Rep. at 89 ("The recent analysis of African-American and White women by Davis et al. showed that both African-American and White women have elevated risk of ovarian cancer if they had used talcum powder products in the genital area.").

205 Davis 2021 at OF6 (reporting an OR for African-American women of 1.22 (95% CI 0.97-1.53)).

Pointing to the fact that many studies have "ORs > 1 and overall consistent values" without accounting for their lack of significance[206] is a one-sided and self-serving approach to statistical significance. While there may be examples where too much weight is placed on statistical significance, it is at least as problematic to ignore it altogether. Contrary to plaintiffs' experts' suggestions, science has not abandoned statistical significance and p-values. I note for example that the journal Nature, which ran an opinion piece by Sander Greenland, who is cited in the reports of multiple plaintiffs' experts for his views on statistical significance, itself stressed that it did not intend to "change how [the journal] considers statistical [significance]."[207] In a similar manner, the New England Journal of Medicine reaffirmed its requirement that authors submit p-values for any principal endpoint in studies they seek to publish in that journal; and while it also announced that it would not impose such a requirement for secondary endpoints, the journal made clear that this was because of a propensity of p-values to detect ***false-positive*** findings,[208] which is essentially the reverse of what plaintiffs' experts are suggesting here. Perhaps for these reasons, there are also a number of scientists who advocate that the standards for statistical significance should be more rigorous, not less.[209] In short, science simply does not accept the suggestion that statistical significance can be ignored when it stands in the way of a desired reading of epidemiological data.

Specificity Is Not Compelling.

Specificity was not considered very important by most of plaintiffs' experts, and I agree.[210] Dr. Wolf states in her report that the "most compelling disease associated with talcum powder use is epithelial ovarian cancer."[211] But ovarian cancers (including epithelial ovarian cancers) comprise a group of distinct diseases that involve distinct tissues of origin and distinct risk factors, which led Dr. McTiernan to recognize specificity is only partially met.[212] Thus, there is no compelling case for specificity here either.

---

206 Singh Supp. Rep. at 20; *see also* Siemiatycki 2nd Am. Rep. at 70 (consistency met because there are many "RR[s] greater than the null value of 1.0").

207 Significant debate. Nature. 2019;567:283.

208 Harrington D, D'Agostino RB, Gatsonis C, et al. New Guidelines for Statistical Reporting in the Journal. *The New England Journal of Medicine*. 2019;381(3):285-286. ("When P values are reported for multiple outcomes without adjustment for multiplicity, the probability of declaring a treatment difference when none exists can be much higher than 5%.").

209 Benjamin DJ, Berger JO, Johannesson M, et al. Redefine Statistical Significance. *Nature Human Behaviour*. 2018;2:6-10.

210 Smith-Bindman 2nd Am. Rep. at 34-35; Cote Rep. at 36 ("Overall, while I think the literature provides support for specificity, I would give this factor a lower weight."); Singh Supp. Rep. at 21 ("I placed less weight on absolute specificity of the association.").

211 Wolf 2nd Am. Rep. at 18.

212 McTiernan 2nd Am. Rep. at 90 (giving moderate weight to specificity and noting it is only met for "certain subtypes" and epithelial ovarian cancer overall). Dr. Smith-Bindman also recognizes the critical distinctions between the types of epithelial ovarian cancers. *See* Smith-Bindman 2nd Am. Rep. at 7 ("Ovarian cancers (epithelial and non-epithelial) are a heterogeneous group of malignancies that vary in their pathological appearance, molecular biology, risk factors, etiology and prognosis. . . . Epithelial ovarian cancers have several histologic types . . . .").

The Epidemiological Data Do Not Show Biological Gradient (Dose-Response).

Available Epidemiological Data On Dose-Response

Evidence of dose-response – i.e., whether the risk of developing ovarian cancer increases with increased perineal talc exposure – is one of the most important factors to consider in evaluating causation. The epidemiological literature studying talc and ovarian cancer has failed to show a dose-response relationship. Plaintiffs' experts claim that there is sufficient data supporting the existence of a dose-response relationship[213] and have pointed to some studies as purported evidence of dose-response, including, for example, the articles by Schildkraut and Cramer.[214] But overall, the literature is very inconsistent with regard to dose-response, as many of plaintiffs' experts concede.[215]

None of the cohort studies based on analysis of actual data (Gonzalez 2016; Houghton 2014; and Gates 2010/Gertig 2000) identified a dose-response relationship, and only a handful of case-control studies (Harlow et al. 1992; Cramer 2016 and Schildkraut 2016) have purported to find one. The case-control studies have in fact shown a wide variety of findings, including: (1) a positive dose-response; (2) no dose-response; (3) a negative dose-response; and (4) a haphazard or bizarre pattern. Notably, among the numerous case-control studies that have not reported a dose-response relationship are several studies that have analyzed "cumulative" talc use (otherwise known as "frequency times duration" of use). For example, Mills 2004 examined cumulative dose by quartiles and reported risks of 1.03, 1.81, 1.74 and 1.06 for ascending quartiles – a bizarre trend that does not support the existence of a dose-response.[216] Similarly, the Cook 1997 study looked for an association across various strata of "cumulative lifetime days."[217] The results showed no statistically significant elevated risk for any of the four categories, with the relative risk for the lowest group (fewer than 2,000 cumulative days, RR 1.8 (95% CI: 0.9-3.5)) essentially matching that of the highest group (greater than 10,000 cumulative days, RR 1.8 (95% CI: 0.9-3.4)).[218] Moreover, as noted above, the Rosenblatt 2011 study looked at the association across four categories of increasing lifetime applications and reported the lowest associations (in fact, negative associations) for its two highest use categories.[219] In addition,

---

213 McTiernan 2nd Am. Rep. at 91-92; Siemiatycki 2nd Am. Rep. at 48-49; Plunkett 2nd Am. Rep. at 55; Cote Rep. at 37.

214 Plunkett 2nd Am. Rep. at 55; Wolf 2nd Am. Rep. at 18.

215 Smith-Bindman 2nd Am. Rep. at 43-44; *see also* Wolf 2nd Am. Rep. at 18 (noting "[m]any of the studies did not obtain the necessary information to evaluate dose response and lacked adequate power to assess dose-response accurately" and there are "limitations of the data"); Cote Rep. at 37 (recognizing "[p]erineal talc exposure is difficult to measure" and "the amount of perineal talc used is not quantified" meaning it "would not be possible to determine in epidemiologic studies" the most relevant exposure metric); Singh Supp Rep. at 21 ("I find biological gradient less compelling."). Prior versions of Dr. Smith-Bindman's reports expressly acknowledged that study results were inconsistent and insufficient to find a dose-response relationship. *See* Smith-Bindman Am. Rep. at 43-44 ("The data from reviewed studies were too diverse to summarize a dose-response relationship."); Smith-Bindman Nov. 15, 2018 Rep. at 40 (acknowledging dose-response results "are inconsistent").

216 Mills 2004.

217 Cook 1997 at 463.

218 *Id.*

219 Rosenblatt 2011 at 740.

Chang found an inverse relationship with risks related to use per month of 1.8, 1.1 and 0.9 for respectively <10, 10-25 and more than 25 applications; similar inverse findings for years of use were 1.7, 1.4 and 0.86 for <30, 30-40 and >40 years of use.[220]

Although some studies have purported to observe a dose trend with cumulative use, those results are not meaningful. For example, the Schildkraut study only compared women who had used talc fewer than 20 years versus more than 20 years and fewer than 3,600 applications versus more than 3,600 applications.[221] Although it found statistically significant associations for the higher but not lower use categories, the study provides little useful information about dose-response because exposure is crudely dichotomized into just two categories each for frequency and duration. And the Cramer study found essentially no difference – and certainly no steady increase – in risk as to women who had (as the study calculated) used talc for the equivalent of 1-5 years, 5-20 years and more than 20 years (odds ratios of 1.36, 1.41 and 1.39, respectively).[222]

Several meta-analyses and pooled studies have analyzed the body of studies and resoundingly concluded that there is not a demonstrated dose-response. For example, the 2013 Terry pooled study of eight case-control studies addressed the potential association between ovarian cancer and the use of powder (broadly defined to include both talc and cornstarch).[223] One of the primary goals of the analysis was to determine whether a dose-response relationship existed, as previous evidence "ha[d] been inconsistent."[224] The authors found that it did not.[225] Indeed, although plaintiffs' experts generally cite this study as evidence supporting a dose-response relationship,[226] the authors stated that they "observed ***no significant trend in risk with increasing number of lifetime applications***."[227] The Terry study, in fact, only observed a positive dose trend when including non-talc users in the analysis,[228] which is not actually meaningful evidence of a dose-response, since including nonusers in a dose-response analysis makes that analysis redundant with whether there is an association with ever/never use. Of note, the Terry authors did not mention the trend with nonusers in their abstract or discussion, instead highlighting that they found "no significant [dose] trend" and explaining that "[w]hether risk increases with number of genital powder applications and for all histologic types of ovarian cancer . . . remains uncertain."[229] The authors also acknowledged that, if anything, the study might ***overstate*** the relationship between powder use and ovarian cancer if cases [i.e., women

220 Chang & Risch 1997.

221 Schildkraut 2016 at 1415-1416 (Table 2).

222 Cramer 2016 at 337 (Table 1).

223 Terry 2013 at 812.

224 *Id.*

225 *Id.*

226 Wolf 2nd Am. Rep. at 18; Plunkett 2nd Am. Rep. at 55.

227 Terry 2013 at 811, 812 (emphasis added).

228 *Id.* at 817.

229 *Id.* at 811, 819-20.

with ovarian cancer] were more likely to report genital-powder use than controls [i.e., women without ovarian cancer]."[230]

Similarly, a 2008 meta-analysis identified "the absence of clear exposure-response associations in most studies" as a crucial piece of missing evidence needed to establish causation.[231] One of the most recent publications reporting on pooled data, Davis 2021 (co-authored by plaintiffs' expert Dr. Moorman) concluded that "there was not a dose–response relationship between frequency or duration of genital powder use and ovarian cancer risk."[232] And in assessing the body of literature, the National Cancer Institute ("NCI") and the United States Food & Drug Administration ("FDA") have respectively concluded that "a dose response relationship was not found" and that "dose-response evidence is lacking."[233] Although two other meta-analyses claimed to find evidence of a very small dose-response, these data are not compelling. Specifically, Berge 2018 reported a "weak" dose-response trend, but cautioned that these data came from a small number of case-control studies.[234] And Penninkilampi divided talc users into only two categories (greater and fewer than 3,600 lifetime applications), finding only a "slightly greater increased risk" for the former category (also based only on case-control data).[235] As with Schildkraut, the arbitrary dichotomous categorization of lifetime use further undercuts the significance of this finding.

Plaintiffs' experts have pointed to the Woolen 2022 meta-analysis on supposed "frequent" talc use as supposed evidence of a dose-response.[236] However, the authors utilized an arbitrary metric of talc exposure (2x or more per week) that did not even map onto the exposure frequencies reported in the underlying studies. The heterogeneity in exposure assessments by the studies renders any attempt at making a dose-response conclusion impossible. Moreover, Woolen 2022 did not undertake any comparative analysis or construct a pooled risk estimate for "less frequent" exposure. In a final attempt to locate a dose-response, plaintiffs' experts claim

---

230 *Id.* at 820.

231 Langseth 2008 at 359; *see* Gertig 2000 at 249, 251 (cohort study concluding that "[w]e did not observe a dose-response relationship with talc use, and previous studies have been inconsistent in this regard"); Cramer 1999 at 355 (case-control study by Dr. Daniel Cramer conceding that "[t]he most obvious weakness in the argument for biologic credibility of the talc and ovarian cancer association is the lack of a clear dose response" and that "[m]ost talc and ovarian cancer studies that have addressed dose response, including this one, have failed to demonstrate consistent dose response relationships").

232 Davis 2021 at OF8.

233 National Cancer Institute. Ovarian, Fallopian Tube, and Primary Peritoneal Cancer Prevention (PDQ)-Health Professional Version, updated October 16, 2023. https://www.cancer.gov/types/ovarian/hp/ovarian-prevention-pdq; Letter from Food & Drug Administration, U.S. Department of Health and Human Services, to Samuel S. Epstein, M.D., Cancer Prevention Coalition, University of Illinois (Apr. 1, 2014); International Agency for Research on Cancer, Monographs on the Evaluation of Carcinogenic Risks to Humans Vol. 93: Carbon Black, Titanium Dioxide, and Talc 18-19 (2010) ("IARC Talc Monographs") (concluding that evidence of a dose-response relationship was "inconsistent").

234 Berge 2018 at abstract, 255.

235 Penninkilampi 2018 at 45.

236 McTiernan 2nd Am. Rep. at 91 (claiming Woolen 2022 "strongly supports a dose-response relationship"); Plunkett 2nd Am. Rep. at 55; Smith-Bindman 2nd Am. Rep. at 35; Siemiatycki 2nd Am. Rep. at 48.

that partial supplemental data from the NHS study shows a dose-response,[237] but unpublished data from a partial subset of a single cohort is too limited to reach such a conclusion.

Consistent with these results, pathological studies have not reported a correlation between the amount of talc used and talc particle counts in ovaries. As one study explained: "ovarian talc particle burden has been found not to correlate with the reported number of lifetime applications, which (if not reflective of inaccurate reporting) may indicate that duration of the powder use is not relevant when assessing risk associated with differing levels of exposure to talc."[238]

In sum, the findings of so many different patterns, or lack of patterns, by dose-response estimation weighs against causation, and indeed, the fact that the data show no clear dose trend is consistent with there being no causal relationship. If one were to believe that perineal talcum powder use causes ovarian cancer, these mixed and inconsistent results should cast serious doubt on the validity of the measures used to estimate whether and how much talcum powder was used.

Validity Of Exposure Measure

In epidemiologic research, it is critical to assess exposures of interest with accuracy and precision. This includes measuring exposures with tools that have demonstrable validity. Without a validated measure of exposure, it is not possible to know whether or not an exposure occurred, and even if it did, it is not possible to quantify the exposure with any degree of certainty.

While there is a scientific approach for development and testing of survey questions for use in research,[239,240,241] there is not a single epidemiologic study of the potential association between perineal use of cosmetic talcum powder and ovarian cancer that has used, or purports to have used, a validated measure of talcum powder use.[242] Thus, it is unknown whether any of the studies has accurately assessed whether talcum powder was used, for how long and how frequently. Self-reported measures can be highly inaccurate, and none has been shown to be

---

237 Plunkett 2nd Am. Rep. at 55; Smith-Bindman 2nd Am. Rep. at 35.

238 Rosenblatt 2011 at 742 (discussing Heller DS, Westhoff C, Gordon RE, Katz N. The Relationship Between Perineal Cosmetic Talc Usage and Ovarian Talc Particle Burden. *American Journal of Epidemiology*. 1996;174(5):1507-1510 ("Heller 1996")).

239 *See generally* Aday LA, Cornelius LJ. Designing and Conducting Health Surveys: A Comprehensive Guide. 3rd ed. San Francisco, CA: 2006.

240 Fowler FJ. Applied Social Research Methods: Survey research methods, 4th ed. (Thousand Oaks, CA: SAGE Publications Ltd). DOI: 10.4135/9781452230184.

241 Seifert B. Validity criteria for exposure assessment methods. *The Science of the Total Environment*. 1995;168(2):101-107.

242 Plunkett 2nd Am. Rep. at 55 ("The human studies do not provide a measure of a single dose in terms that are typical of the cellular (*in vitro*) or animal studies, *i.e.*, mg talc per kg body weight, or mg talc per m^3 inhaled air, or mg talc per ml of solution."); Wolf 2nd Am. Rep. at 18 ("Exposure is difficult to quantify with talcum powder applications with regard to how much is used, where it is concentrated, and how much actually reaches the tubes and ovaries."); Cote Rep. at 37 ("While number of applications and years of is a straightforward way to assess dose (i.e., frequency of use multiplied by years of use), the amount of perineal talc used is not quantified."); Singh Supp. Rep. at 21 (noting study design limitations regarding "specificity of dosing of talc" render evidence of "biological gradient less compelling").

valid. In studies of medication use, for example, validation of self-report can come from examining pharmacy dispensation records or deploying electronic counters to medications as objective measures to validate a person's reported use of a medication. No such efforts have gone into the development of questions about self-reported talc use.

Even more important, perhaps, is that no study has used a measure that has been shown to estimate the relevant dose of talcum powder. An "application" of talcum powder has no standard definition. It is unknown how much, if any, talcum powder reported on any of the questionnaires is applied to the perineum, how much, if any, reached the vagina, nor how much, if any, reached the ovaries.[243] This problem is especially profound in this context, because slight inaccuracies in estimating the amount used on a daily basis could significantly alter total estimated use where the history in some cases spans multiple decades. Thus, it is impossible from the studies to determine how much, if any, talcum powder was applied to the perineum, and likewise impossible to measure how much, if any, talcum powder migrated into the vagina, across the cervix, up through the uterus and eventually reached the ovaries, as Dr. Cote has recognized.[244] At best, the wide variety of non-validated measures of talcum powder use can collect hypothesis-generating data, and there is no assurance that any estimates of talc use are accurate or valid.

Below is an example of the challenges presented when a validated measure of exposure is nonexistent:

> Consider the question of whether or not consumption of milk can either cause or protect against the development of allergies. It might seem simple that one could design a survey to ask people, with and without allergies, about their past consumption of milk. A question could be: in the past 12 months, did you drink milk? People with and without allergies could be compared by whether or not they drink milk. But does the development of allergy depend on the amount of fat in the milk? In that case, we need to ask if the milk was whole milk, skim milk, 1%, or 2% fat? And does the person only drink one of those types of milk or multiple types of milk? Perhaps a person drinks 2% milk, but uses half-and-half in their coffee. So, we would need questions to understand that. In case people change their milk preferences over time, we might need questions to determine at what ages the person drank whole milk, for example, and then when did they start also drinking skim milk.
>
> But what if the issue of allergy is related to protein in milk? Then we need to be able to assess any other beverages and foods that contain milk protein. We cannot simply ask about milk. The range of foods that include milk protein is tremendous and includes yogurt, milkshakes, and breads. Among breads alone, milk protein can be found in loaves of bread, biscuits, donuts, crackers, pancakes, waffles, French toast and others. Milk protein can be found in other foods, too, such as cereals and desserts, including cake,

---

[243] Wolf 2nd Am. Rep. at 18 ("Exposure is difficult to quantify with talcum powder applications with regard to how much is used, where it is concentrated, and how much actually reaches the tubes and ovaries."); Cote Rep. at 37 ("It is likely the amount of talc that can travel up into the reproductive tract that is most important, and that measurement would not be possible to determine in epidemiologic studies.").

[244] Cote Rep. at 37 ("It is likely the amount of talc that can travel up into the reproductive tract that is most important, and that measurement would not be possible to determine in epidemiologic studies.").

> cookies, pudding, ice cream and pastries. Milk protein may be in scrambled eggs, butter, cream and margarine, salad dressing and even some "non-dairy" creamers. The list of foods that include milk proteins goes on and on, even including meat products such as sausage, vegetables prepared *au gratin* or with butter or cream, candy including chocolate and many soups, chowders and bisques.
>
> It should be apparent that our simple question about milk is far more complicated than whether or not one drinks milk.
>
> Once we have identified all of the foods and beverages we need to ask about, we still need to determine the amount, or "dose," of milk consumed. This step can be very difficult. If you ask about eating soup that may have milk in it, how do you quantify if? A cup or a bowl? How big is the cup? Is the cup full to the top or about 2/3 of the way up? How much milk is in a "glass" of milk? We might need some tools to use, such as food models or empty containers, to show the person telling us the amount they consumed.
>
> And then if we agree on a way to standardize the size of a portion of soup or milk, how do we know that people are accurately reporting when they say they typically drink 3 glasses of milk per week? The answer is: if we want to come close to knowing the truth, then we have to demonstrate the validity of the questionnaire.

The validation process is separate from the research study and typically enrolls other people for the sole purpose of determining whether and how well the questionnaire works. One method is to ask people to fill out very detailed food diaries for a few different days (in nearly real-time as they are eating and drinking, so the information is fresh) and then compare how those same people answer a question a week later about what they consumed over the past week. The extent to which the answers using the two methods are in agreement provides evidence for the validity of the survey questions. Other approaches include asking people to take pictures of what they eat to use for validation. The main point is that there is a formal process of determining the validity of survey questions that is necessary if one wants to collect high quality data and be able to approximate the truth.

Certain of plaintiffs' experts have raised related issues in their critiques of the evidence for and against a dose-response relationship.[245] However, these same issues of validity of the exposure measure are just as important for assessing the overall proposition of whether or not talcum powder causes ovarian cancer. For example, Dr. Cote criticizes the cohort studies for examining any talc use (which she claims "did not have detailed exposure information").[246] But if plaintiffs' experts believe the cohort studies suffer from assessing "any" use, that criticism should apply even-handedly to the case-control studies and meta-analyses (such as the Penninkilampi study) that did the same. As Dr. Smith-Bindman observes, the Terry study (which she and other plaintiffs' experts rely on in support of their dose-response opinions) reported that the prevalence of powder use by controls in the underlying studies ranged from 15 to 45 percent, which she attributes to "variation in the definition of powder use" in the underlying studies it

---

[245] McTiernan 2nd Am. Rep. at 91-92; Siemiatycki 2nd Am. Rep. at 48-49; Plunkett 2nd Am. Rep. at 55; Cote Rep. at 37.

[246] Cote Rep. at 27.

examined.[247] Her point affirms concern about the validity of talc exposure assessment and that the magnitude of error could be tremendous. But cohort studies are not uniquely subject to exposure assessment problems, and it is inappropriate for plaintiffs' experts to criticize them for this reason while ignoring similar issues with case-control studies.

Further highlighting the importance of using validated measures of exposure, Dr. Graham Colditz, a frequent plaintiffs' expert in talc litigation, described the evolution of the Nurses' Health Study and noted that "there have been continuing efforts to validate questionnaire-based exposure measures used in the study."[248] For example, in order to measure nutritional exposures that might be relevant to cancer and other disease risks, Dr. Colditz noted that "[a]ssessment of long term diet is necessary to relate nutrient intake to the risk of chronic diseases," and that "this is best accomplished through the use of a food-frequency questionnaire." Further, he stated that the "Nurses' Health Study investigators have devoted great attention to the development, evaluation and refinement of food-frequency questionnaires for epidemiological applications." There were no such efforts employed in the NHS, nor in any other study, to develop and validate measures of talcum powder use.

Other authors have repeatedly discussed the limits of exposure measures in the epidemiologic studies. For example, in Schildkraut, the authors stated: "A recent publication of data from the WHI, which did not find an association with genital talc use and ovarian cancer, was accompanied by an editorial that emphasized the challenges in assessing the exposure to talc due to reliance on self-report. This limitation in the measurement of the exposure variables in the current study needs to be considered when interpreting our results."[249] The Berge authors noted as a limitation to their meta-analysis that "neither the definition of the exposure of interest (genital talc use) nor the strategy for adjustment for potential confounders were fully consistent across studies."[250] Another limitation was the "self-reported information on the main exposure of interest, with no external validation."[251] In the Langseth (2008) paper, the authors noted that "the current body of epidemiologic evidence is insufficient to establish a causal association between perineal use of talc and ovarian cancer risk," and pointed to the "crudeness of the exposure metric used," and that "it is important that future studies, irrespective of study design, devote some effort to better assessment of exposure."[252] This "crudeness" of the exposure measure was apparent in Terry (2013) as the authors needed to define genital powder use as "any type of powder (talc, baby, deodorizing, cornstarch or unspecified/unknown)" and acknowledged that a study limitation was "differences in the wording of questions about genital powder use between studies."[253] In the same vein, another author cautioned that composition of body powders varies from one brand to the next. Thus, "[d]ata from additional cohort studies would be welcome, but

---

247 Smith-Bindman 2nd Am. Rep. at 27.

248 Colditz GA, Hankinson SE. The Nurses' Health Study: lifestyle and health among women. *Nature Reviews Cancer*. 2005;5(5):388-396 ("Colditz 2005").

249 Schildkraut 2016 at 1416.

250 Berge 2018 at 255.

251 *Id.*

252 Langseth 2008.

253 Terry 2013 at 812, 820.

without details concerning the composition of the powders used by cohort members—details that many participants may not be able to provide—the results of such studies may be similarly ambiguous in their interpretation."[254] Dr. Cramer, a plaintiffs' expert in prior talc cases, similarly acknowledged that "[t]here are inherent limitations in quantifying a dose-response due to a lack of metrics for how much talc is in an 'application,' how much enters the vagina, and how much reaches the upper genital tract where, presumably, any deleterious effect is mediated."[255] Many other authors have expressed similar concerns pertaining to the accuracy of exposure measurements.[256]

In sum, without a validated measure of talcum powder use, it is impossible to correctly determine whether or not an exposure occurred or the quantity of purported exposure, making it impossible to reliably conclude that there is a causative relationship between perineal talcum powder use and ovarian cancer based on the current literature.

The Epidemiological Data Do Not Demonstrate Temporality

The strongest evidence for temporality comes from studies that assess the exposure at one point in time, and then assess the outcome at a future time. The prospective cohort studies are the only studies examining a potential connection between talc use and ovarian cancer that do that and thus represent the best evidence to assess temporality. As described more fully above, the cohort studies failed to show an association of ovarian cancer with talcum powder use. The case-control studies ask about past exposure, but they ask those questions at the same time that the outcome is already known. Temporality is assumed in case-control studies, though it is not a fact, as it is in cohort studies (or clinical trials). That is the reason that recall errors and recall bias are such a concern in case-control studies. Unlike prospective studies, subjects need to accurately remember and report past exposures. Recall bias occurs when people with a disease, compared to those without a disease, report different exposure histories compared to the truth. Specifically, people with a disease may be more likely to recall or report exposures than those without the disease, which can inflate the apparent risk. This distortion is especially important when measured risks are low.

While it is a different concept from temporality, latency is a concept that is important to consider when evaluating temporality. Latency is the time from exposure to development of disease. When latency is known, one would want to make sure that not only did the exposure

---

254 Rosenblatt 2011.

255 Cramer 2016 at 344.

256 Gonzalez 2016 ("one challenge with studying talc is that the chemical formulation of talc has changed over time, and not all powders contain the mineral talc"); Cook 1997 ("it is not clear how ascertainment of perineal powder application correctly estimates actual exposure to particles in powder that may influence ovarian cancer risk"); Mills 2004 at 463 ("the lack of dose response between talc use and EOC may be explained by the inability to quantify the actual amount of talc used per application and timing of the application"); Rosenblatt 2011 ("[The validity of all these studies, including ours, may be influenced by the level of non-response among cases and controls, and by the potential for misclassification (differential and non-differential) of exposure status. The latter derives not just from errors in the recall of the use of genital powder, but from the fact that the presence or concentration of talc can vary from brand to brand and even within one brand of powder over time. Therefore, even when respondents are asked specifically about perineal exposure to powders that contain talc (as in our study), they may be unable to provide accurate information.").

occur in the past, but that it occurred long enough ago in the past that a cancer would have time to develop. Obviously, without determining whether or not talcum powder causes ovarian cancer, it is not possible to state that there is a known latency. Nonetheless, Dr. Wolf states that the average latency period between exposure to talc and diagnosis of ovarian cancer is at least 20 years, citing two articles[257,258] that do not examine this issue.[259] Based on this theory, Dr. Wolf and, less directly, plaintiffs' other experts, have stated that a limitation of the cohort studies is that they might not have been of sufficient length to capture latency.[260] Obviously, without a known latency period, that concept is only speculative. Moreover, as explained above, the cohort studies have accounted for decades of talcum powder use. Thus, if women started using talcum powder at approximately 20 years old[261] and the latency period is approximately 20 years,[262] then both the Women's Health Initiative Study and Sister Study would account for a sufficient latency period. Regardless, as mentioned above, O'Brien 2020 added years of follow-up time for the cohort studies included therein but still found no association between talc use and ovarian cancer despite addressing plaintiffs' experts' concerns over latency.

The Epidemiological Data Lack Coherence.

Dr. Hill stated that the cause and effect interpretation of the data "should not seriously conflict with the generally known facts and the biology of the disease." Dr. Hill cited the example of temporal trends in the rise in lung cancer rates while smoking was increasing. But here, there are no published studies that have demonstrated any such ecological coherence with talcum powder and ovarian cancer. Specifically, I can find no published studies that have examined trends in ovarian cancer rates in relation to trends in talcum powder use. Dr. Hill also cited, as an example of coherence, the changes of bronchial epithelial cells in smokers. But again, here there are no studies that have demonstrated histopathological differences in ovaries of talc users and non-users (nor in any tissues of the female genital tract). The lack of such evidence strongly argues against coherence.

No Experimental Evidence.

There is no experimental evidence of any relationship between talcum powder use and ovarian cancer in humans in the sense of randomized controlled trials, as plaintiffs' experts

---

257 Purdie DM, Bain CJ, Siskind V, et al. Ovulation and risk of epithelial ovarian cancer. *International Journal of Cancer*. 2003;104:228-232.

258 Okada, F. Beyond foreign-body-induced carcinogenesis: Impact of reactive oxygen species derived from inflammatory cells in tumorigenic conversation and tumor progression. *International Journal of Cancer*. 2007;121:2364-2372.

259 Wolf 2nd Am. Rep. at 18.

260 *Id.* at 8-9; Smith-Bindman 2nd Am. Rep. at 17 (asserting that a limitation of the cohort studies is "very short follow-up periods" without referencing latency specifically); McTiernan 2nd Am. Rep. at 53-54; Siemiatycki 2nd Am. Rep. at 63.

261 Cramer 2016 at 335.

262 Wolf 2nd Am. Rep. at 18.

agree.[263] Plaintiffs' experts variously refer to laboratory animal and *in vitro* testing,[264] experimental evidence "involving migration of talc" or "the inflammatory process"[265] but this evidence is better addressed under the rubric of biological mechanism, which is the topic to which each relates.

The Epidemiologic Data Are Not Analogous.

Plaintiffs' experts opine that talcum powder's similarity to asbestos offers an appropriate analogy,[266] but asbestos and talc are distinct minerals, with distinct elemental composition and morphology, and it cannot simply be assumed that epidemiological study of asbestos can be applied by analogy to the case of talc, especially in light of the fact that talc itself has been extensively studied and its epidemiological literature reports vastly different risk levels than the asbestos literature. In particular, the talc/asbestos analogy is unpersuasive because talc exposure is not associated with an increased risk of mesothelioma or lung cancer (diseases caused by asbestos), and as set forth below, it has not been shown that asbestos causes ovarian cancer. In addition, simply stating that a mineral causes one type of cancer, and it therefore causes another type of cancer, is highly simplistic and unscientific. Moreover, the limited analogy arguments that Dr. Smith-Bindman advances do not make sense. She refers to talc's "fibrous nature," even though platy talc is not fibrous, and she further essentially concedes that the talc-ovarian cancer evidence is "weak[]" in making the unsupported claim that "weaker evidence" should suffice to prove causation when there is an appropriate analogy.[267]

Dr. Wolf likens talc not only to asbestos but also to "various and specific carcinogens" such as smoking, sun exposure and human papilloma virus, claiming that all of these agents promote "an inflammatory process" that causes cancer.[268] This "analogy" operates at such a high level of generality as to be useless. As elaborated in the next section, there are any number of other sources of inflammation that do not cause cancer, and the evidence cited in support of the conclusion that talc causes inflammation in the ovaries or that such inflammation could be carcinogenic is weak and significantly undercut by contrary evidence. In short, analogy has not been established.

The Evidence For A Biological Mechanism By Which Talc Could Cause Cancer Is Weak.

Plaintiffs' experts generally propose that talc or alleged other constituents in talcum powder (e.g., asbestos, heavy metals or fragrance chemicals) can travel from the perineum up the genital tract to the ovaries – against gravity and the downward flow of vaginal mucous and

---

263 McTiernan 2nd Am. Rep. at 93 ("[H]ere, randomized controlled trials are neither feasible nor ethical"); Wolf 2nd Am. Rep. at 19; Cote Rep. at 38; Smith-Bindman 2nd Am. Rep. at 36.

264 Wolf 2nd Am. Rep. at 19; Plunkett 2nd Am. Rep. at 32.

265 McTiernan 2nd Am. Rep. at 93; *see also* Plunkett 2nd Am. Rep. at 32; Smith-Bindman 2nd Am. Rep. at 36.

266 McTiernan 2nd Am. Rep. at 91; Siemiatycki 2nd Am. Rep. at 72; Smith-Bindman 2nd Am. Rep. at 36; Singh Supp. Rep. at 23.

267 Smith-Bindman 2nd Am. Rep. at 36.

268 Wolf 2nd Am. Rep. at 19-20.

menstrual fluids.[269] They also suggest an alternative pathway, via inhalation and the lymphatic system.[270] These proposed mechanisms are speculative and unsupported by science.

Studies Have Repeatedly Stated That Scientific Evidence Is Insufficient To Show Mechanisms Of Talc-Based Ovarian Carcinogenesis.

As an initial matter, based on my review of the available epidemiologic literature, many authors of studies have made clear that the evidence is insufficient to understand any purported mechanism by which talc-based cosmetic powders could cause ovarian cancer. This is directly contrary to the claims made by Dr. Wolf in her report.[271] For example:

Taher (2019)[272]

> "[T]alc is not genotoxic."
>
> While there is "some evidence" supporting the notion that talc can migrate to the ovaries, that evidence is "inconsistent."

Penninkilampi (2018)[273]

> "[T]he potential mechanism by which genital talc is associated with an increased risk of ovarian cancer hence remains unclear."
>
> "[U]nfortunately, the evidence remains insufficient to understand the mechanisms with any reasonable certainty."
>
> "[T]here is a substantial need for further research on a potential mechanism."

Berge (2018)[274]

> "[T]he biological basis and plausibility of a possible carcinogenic effect of talc on the ovaries is still not understood and remains questionable."

---

269 Plunkett 2nd Am. Rep. at 29-40; Smith-Bindman 2nd Am. Rep. at 36; Wolf 2nd Am. Rep. at 12-13; Siemiatycki 2nd Am. Rep. at 71.

270 McTiernan 2nd AM. Rep. at 92; Plunkett 2nd Am. Rep. at 29-30; Wolf 2nd Am. Rep. at 13, 18-19.

271 Wolf 2nd Am. Rep. at 19 ("[I]t is my opinion that the genital use of talcum powder can cause ovarian cancer. In recent years, other scientists, physicians, and organizations have reached this same conclusion.").

272 Taher 2019 at 94, 96.

273 Penninkilampi 2018 at 11-12, 14.

274 Berge 2018 at 255.

Cramer (2016)[275]

> "[U]nfortunately, no epidemiologic study of epithelial ovarian cancer and talc has taken the opportunity to determine whether talc can actually be found in tissues removed at surgery and correlated with exposure to talc."

Terry (2013)[276]

> "[T]he biological plausibility for the observed association between genital powder use and ovarian cancer has been challenged because evidence for dose-response has been inconsistent."
>
> "[L]ittle is known about the biologic effects of genital powder use."
>
> "[M]ore work is needed to understand how genital powders may exert a carcinogenic effect, and which constituents (e.g., talc) may be involved."

Gates (2008)[277]

> "The association remains controversial due to the lack of a clear dose-response with increasing frequency or duration of talc use, the possibility of confounding or other biases, and the uncertain biological mechanism."

Merritt (2008)[278]

> "[T]hese results in combination with previous studies suggest that chronic inflammation is unlikely to play a major role in the development of ovarian cancer."

Mills (2004)[279]

> "[R]esearch has provided little biologic or experimental evidence to support a relationship between talcum powder use and ovarian cancer risk."

Whittemore (1988)[280]

> "While these findings indicate that vaginal exposure to particulates can lead to deposition on the ovaries, they do not implicate such exposure in ovarian carcinogenesis, and data relating directly to this possibility are needed."

---

275 Cramer 2016 at 344.

276 Terry 2013 at 819-20.

277 Gates 2008 at 2437.

278 Merritt 2008 at 174.

279 Mills 2004 at 464.

280 Whittemore 1988.

As these excerpts make clear, plaintiffs' experts' suggestion that there is "extremely strong evidence"[281] of biological plausibility or that a biological mechanism is "established" and "well-accepted"[282] is simply false.

Scientific Study Does Not Support The Inhalation Or Migration Theories By Which Talc Is Supposed To Reach The Ovaries.

Scientific data also fail to demonstrate a plausible mechanism by which talc or accessory particles could physically reach the ovaries from external use.

Plaintiffs' experts principally suggest that talc and asbestos particles can travel from the perineum up the genital tract to the ovaries – against gravity and the downward flow of vaginal mucous and menstrual fluids.[283] The results of research addressing retrograde transport have been inconclusive.[284] For example, one study examining the amount of talc in the ovaries of women who had undergone surgery for benign ovarian neoplasms found no correlation between the women's talc use and their talc particle counts.[285] Another study reviewed pathology slides from 213 ovarian tumors and found definite silicate crystals in only five patients, which may have reflected talc contamination from surgical gloves.[286] And as noted by IARC, while some studies of potential retrograde movement of particles in women who were about to undergo gynecological surgery for diseases or complications of the reproductive tract or organs have suggested that such transport is possible, "broad interpretations with regard to healthy women" based on these studies "may be limited."[287] Thus, IARC reported that, "[o]n balance, the Working Group believed that the evidence for retrograde transport of talc to the ovaries in normal women is weak."[288]

Relatedly, while plaintiffs' experts point out that talc particles and asbestos fibers have been found in ovarian tissue, this fact is of no scientific significance because researchers have found such particles in the ovaries of women with and without perineal talc use or other known exposures to talc or asbestos.[289] The Heller (1996) study, which many of plaintiffs' experts

---

281 Smith-Bindman 2nd Am. Rep. at 36.

282 Wolf 2nd Am. Rep. at 18.

283 *Id.* at 12 ("[I]t is universally accepted in the gynecologic community that substances [can] migrate and/or be transported [sic] in both directions.").

284 IARC Talc Monographs at 392.

285 Heller 1996.

286 Yaker A, Benirschke K. A ten year study of ovarian tumors. *Virchows Archiv A Pathological Anatomy and Histology*. 1975;366(4):275-86.

287 IARC Talc Monographs at 392.

288 *Id.* at 411.

289 Heller 1996 at 1508, 1510; Heller DS, Gordon RE, Westhoff C, Gerber S. Asbestos exposure and ovarian fiber burden. *American Journal of Industrial Medicine*. 1996;29(5):435-439 (noting that asbestos fibers were found in ovarian tissue of women with and without history of exposure).

cite,[290] found that "talc particles were observed to a similar extent with both exposed and unexposed subjects" and that particles were actually found in higher proportions among women who did not apply talc on the perineum, stating that "[o]ur results do not support a linear dose-related ovarian talc particle burden."[291] As an article co-authored by plaintiffs' expert Dr. John Godleski explains, the Heller article's findings were likely "influenced by contamination" with talc from exogenous sources.[292] In short, the presence of fibers in ovarian tissue does not establish the relevant exposure pathways.

Studies have also failed to show an association between use of talc-dusted diaphragms and condoms and ovarian cancer.[293] Evaluating an association with the use of talc-dusted diaphragms and condoms has been deemed "the most valid method for testing the carcinogenic potential of talc" because "[b]y definition, the female reproductive tract is exposed to talc containing powders introduced by diaphragms, whereas an exposure route based on perineal dusting requires unproven assumptions about vaginal exposure."[294]

Moreover, numerous studies have considered whether tubal ligation and hysterectomy – procedures that purportedly "block the environmental contamination of the ovaries" – are associated with a decreased risk of ovarian cancer among perineal talc users.[295] Although plaintiffs' experts assert that these studies "strongly suggest that the increased risk of ovarian cancer associated with talcum powder products use is reduced or eliminated after tubal ligation or hysterectomy,"[296] my review of the available literature reveals that the results have been inconsistent.[297] In fact, the only cohort study to address this issue found that "[w]omen who were ever talc users and had never had a tubal ligation were not at increased risk of epithelial ovarian cancer compared with women who had not used talc (RR = 0.97; 95% CI = 0.71-1.32)" and "[t]here was no evidence of heterogeneity of RRs between women who had a tubal ligation and women who did not," and thus concluded that "no effect modification was seen by history of

---

290 McTiernan 2nd Am. Rep. at 80; Siemiatycki 2nd Am. Rep. at 71; Wolf 2nd Am. Rep. at 13; Plunkett 2nd Am. Rep. at 37-38; Cote Rep. at 13; Smith-Bindman 2nd Am. Rep. at 31.

291 Heller 1996 at 1508, 1510.

292 McDonald SA, Fan Y, Welch R, et al. Correlative polarizing light and scanning electron microscopy for the assessment of talc in pelvic region lymph nodes. Ultrastructural Pathology. 2019;43(1):13-27, 24.

293 Hartge 1983; Fiume 2015 at 122S ("[S]tudies demonstrating that the use of talc-dusted condoms or diaphragms, which would clearly result in exposure close to the cervical opening, [have found that talc] was generally not associated with increased RR estimates for ovarian cancer."); Muscat & Huncharek 2008 at 5-6 (describing meta-analyses showing no association between use of talc-dusted diaphragms and condoms and ovarian cancer); Penninkilampi 2018 at 42, 44 ("Talc use on diaphragms or on sanitary napkins was not individually associated with increased risk of ovarian cancer.").

294 Muscat & Huncharek 2008 at 5, 9 ("It may be argued that the overall null findings associated with talc-dusted diaphragms and condom use is more convincing evidence for a lack of a carcinogenic effect, especially given the lack of an established correlation between perineal dusting frequency and ovarian tissue talc concentrations and the lack of a consistent dose-response relationship with ovarian cancer risk.").

295 *Id.* at 7.

296 Smith-Bindman 2nd Am. Rep. at 31.

297 Muscat & Huncharek 2008 at 7.

tubal ligation."[298] In the pooled analysis by O'Brien,[299] the authors examined the study subgroup with a patent reproductive tract and found a small statistically significant association [HR 1.13 (95% CI 1.01 to 1.26)]. The authors, though, reported a non-significant interaction when comparing results of women with vs. without patency and concluded that the finding in the patent tract subgroup "should be considered only exploratory and hypothesis generating." A pooled analysis of case-control studies observed similar ovarian cancer associations for talc use in women with tubal ligation or hysterectomy regardless of whether the "exposure to genital powder applications" occurred before or after the surgery.[300] Several case-control studies of talc exposure and ovarian cancer have found a lower incidence of ovarian cancer in patients who used talc and had tubal ligation but a higher incidence in patients who used talc and had hysterectomies,[301] which is a puzzling result since both hysterectomy and tubal ligation should cut off the pathway through which talc could travel to the ovaries. Because tubal ligation and hysterectomy would prevent the migration of talc particles from the perineum, the fact that studies have not consistently shown a reduced risk associated with these surgeries undermines the premise that talc particles travel to the ovaries and cause cancer.

Finally, plaintiffs' experts espouse a theory that talc or accessory particles can reach the ovaries via inhalation (i.e., that women who use cosmetic talc inhale some amount of talc particles while they are applying cosmetic talc).[302] But I have not seen a mechanistic study that demonstrates that inhaled talc particles can reach the ovaries, and plaintiffs' experts do not cite one.[303] Furthermore, while most of the epidemiologic studies did not examine non-perineal application of talcum powder, those that assessed application to other body parts found inconsistent results. For example, although Penninkilampi found a small elevation in risk with "any non-perineal" talc use [1.24 (1.01-1.51)], this finding was limited by the significant heterogeneity across the studies. In the Terry pooled analysis of more than 18,000 women, non-perineal application showed no risk [0.98 (0.89-1.07)]. Likewise, the recent study by Cramer (2016) showed no association of use of powder on the body with ovarian cancer [0.99 (0.84-1.16)]. As plaintiffs' expert Dr. Wolf aptly summarized, these studies by and large show "that there's no carcinogenicity" from body-only powder use.[304] As mentioned above, the Leung 2023 article co-authored by plaintiffs' expert Dr. Siemiatycki found no significant association between

---

298 Gertig 2000 at 251.

299 O'Brian 2020.

300 Terry 2013 at 817.

301 Mills 2004 (finding odds ratios of 0.88 and 1.54 for tubal ligation/no tubal ligation and odds ratios of 1.79 and 1.33 for hysterectomy/no hysterectomy); Cramer 1999 at 352 (odds ratios of 0.98 and 1.80 for tubal ligation/no tubal ligation and 2.61 and 1.60 for hysterectomy/no hysterectomy).

302 McTiernan 2nd Am. Rep. at 92; Plunkett 2nd Am. Rep. at 29-30; Wolf 2nd Am. Rep. at 13, 18-19.

303 At a past deposition, Dr. Wolf suggested that studies reporting talc found in pelvic lymph nodes are supportive of an inhalation route of exposure, although she also testified that talc in "the pelvic lymph nodes could also come from the ovary in the other direction." Wolf 1/7/2019 Dep. 206:6-207:2. As Dr. Wolf's own uncertain testimony reveals, the studies to which she refers are at best hypothesis-generating, and they certainly do not elaborate the mechanism by which talc would reach the ovaries through inhalation.

304 *Id.* 204:16-205:6.

occupational talcum powder use and ovarian cancer. These findings confirm the lack of any purported connection between inhaled talcum powder and ovarian cancer.

The Theory That Talc Can Cause Inflammation That Promotes Cancer Lacks Scientific Support.

The theory asserted by several of plaintiffs' experts that talc particles that reach the ovaries can cause inflammation leading to cancer (the "inflammation theory") also lacks support.[305]

First and foremost, no biological mechanism theory accounts for the fact that talc is not mutagenic or genotoxic.[306] This fact significantly undermines the theory that talc causes ovarian cancer, since gene mutation is widely recognized as what triggers ovarian cancer.[307] In the same vein, animal studies (including studies directly injecting talc into the ovaries of rats) have not shown that prolonged exposure to talc causes ovarian cancer or precancerous changes in ovarian cells.[308] Likewise, in vitro and pathological studies have not shown evidence of talc-induced ovarian cancer.[309]

The inflammation theory is also unsupported and implausible. A study sought to determine whether histological signs of inflammation were associated with ovarian cancer and found "no significant correlation . . . between serous carcinoma and histological signs of inflammation or chronic tubal injury."[310] Studies have not established a causal association

---

[305] McTiernan 2nd Am. Rep. at 81-83; Siemiatycki 2nd Am. Rep. at 71; Wolf 2nd Am. Rep. at 14-16; Smith-Bindman 2nd Am. Rep. at 12-14; Cote Rep. at 14-15; Plunkett 2nd Am. Rep. at 46-53.

[306] Muscat & Huncharek 2008 at 9 (citing Endo-Capron S, Renier A, Janson X, et al. In vitro response of rat pleural mesothelial cells to talc samples in genotoxicity assays (sister chromatid exchanges and DNA repair). *Toxicol In Vitro*. 1993;7(1):7-14); IARC Talc Monographs at 399; Plunkett Nov. 16, 2018 Rep. at 47 (acknowledging that the "evidence show[s] that [talc] is not genotoxic (in most assays)").

[307] Mayo Clinic "Cancer", Last accessed November 28, 2023. https://www.mayoclinic.org/diseases-conditions/ovarian-cancer/symptoms-causes/syc-20375941; Anand P, Kunnumakkara AB, Sundaram C, et al. Cancer is a preventable disease that requires major lifestyle changes. *Pharm Res.* 2008;25(9):2097-2116, at 2098 (noting that "all cancers are a result of multiple mutations").

[308] Muscat & Huncharek 2008 at 9 (lifetime whole body exposure experiments in female laboratory rats found that ovarian tissue was not contaminated with talc and that ovarian tumor incidence was not increased) (citing Boorman GA, Seely JC. The lack of an ovarian effect of lifetime talc exposure in F344/N rats and B6C3F1 mice. *Regul Toxicol Pharmacol.* 1995;21(2):242-243); Hamilton TC, Fox H, Buckley CH, et al. Effects of talc on the rat ovary. *Br J Exp Pathol.* 1984;65(1):101-106 (study exposing rat ovaries to talc finding that the "epithelium covering the papillae was regular with no evidence of cytoplasmic or nuclear atypia"; there was no "evidence of frank neoplasia"; and that observed inflammation was not near the papillae).

[309] Muscat & Huncharek 2008 at 9; IARC Talc Monographs at 397-98; Lee P, Sun L, Lim CK, et al. Selective apoptosis of lung cancer cells with talc. *Eur Respir J.* 2010;35(2):450-452, at 452; Nasreen N, Mohammed KA, Brown S, et al. Talc mediates angiostasis in malignant pleural effusions via endostatin induction. *Eur Respir J.* 2007;29(4):761-769, at 761-762 (in vitro studies reporting that talc stops new blood vessels from forming and causes cell death only in malignant cells, leaving healthy cells alone).

[310] Malmberg K, Klynning C, Flöter-Rådestad A, Carlson JW. Serous tubal intraepithelial carcinoma, chronic fallopian tube injury, and serous carcinoma development. *Virchows Arch.* 2016; 468(6):707-713

between the use of cosmetic talc and cancers in vaginal, uterine and cervical tissue.[311] If talc (or alleged asbestos in talc products) produced inflammatory responses or carcinogenesis in ovarian tissue, it might also produce the same in other tissue.[312] These tissues are closer to the perineum than the ovaries and likely are exposed to greater concentrations of talc than the ovaries. Further evidence of the lack of association of talc and uterine cancer and cervical cancer comes from the Lynch systematic review (as described above).[313] That study found suggestive evidence of no association between genital talc application and endometrial cancer, and insufficient evidence to determine whether there is a causal association between genital talc application and cervical cancer. Results of a pooled analysis of prospective studies of genital powder use and risk of uterine cancer was published in 2021.[314] Pooling data from four prospective cohorts (N=209,185), the authors "did not observe an association between uterine cancer and ever use of powder in the genital area" [HR 1.01, 95% CI 0.94-1.09]. Cervical cancer risk was evaluated in a publication from the Sister Study.[315] While the study did find a positive risk for cervical cancer with self-reported douching, the study "did not see evidence of an association" of genital talc use and cervical cancer.

The lack of evidence showing a reduced risk associated with the use of anti-inflammatory drugs further undermines the inflammation theory. Most meta-analyses examining this issue have found no risk reduction with either aspirin or non-steroidal anti-inflammatory drug ("NSAID") use.[316] One did report a modest risk reduction for aspirin use but found no such reduction for NSAID use.[317] The meta-analysis concluded that "[f]urther biological and

---

311 Smith-Bindman Dep. Vol. II 288:20-24. A publication stemming from the Sister Study reported an association [HR 1.2 (95% CI:0.94-1.6)] between perineal talc use and uterine cancer, but the report stopped short of drawing a causal conclusion from its results and acknowledged that "few studies have examined the association between talc and uterine cancer, even though the uterus is more proximal to the exposure site." O'Brien KM, D'Aloisio AA, Shi M, et al. Perineal Talc Use, Douching, and the Risk of Uterine Cancer. *Epidemiology*. 2019;30(6):845-852, at 845.

312 Smith-Bindman Dep. Vol. II 288:15-19 (admitting she "do[es] not know of" any studies showing inflammation as a result of genital talc use in vaginal, uterine or cervical tissues, among others).

313 Lynch HN, Lauer DJ, Leleck OM, et al. "Systematic review of the association between talc and female reproductive tract cancers." *Frontiers in Toxicology*. 2023;5:1157761. Published 2023 Aug 7.

314 O'Brien KM, Tworoger SS, Harris HR, et al. "Genital powder use and risk of uterine cancer: A pooled analysis of prospective studies." *International Journal of Cancer*. 2021;148(11):2692-2701.

315 O'Brien KM, Weinberg CR, D'Aloisio AA, et al. "The association between douching, genital talc use, and the risk of prevalent and incident cervical cancer." *Scientific Reports*. 2021;11(1):14836.

316 Bonovas S, Filioussi K, Sitaras NM. Do nonsteroidal anti-inflammatory drugs affect the risk of developing ovarian cancer? A meta-analysis. *Br J Clin Pharmacol.* 2005;60(2):194-203 (RR 0.93 (95% CI: 0.81-1.06) for aspirin use; RR 0.88 (95% CI: 0.76-1.01) for NSAID use); Ni X, Ma J, Zhao Y, et al. Meta-analysis on the association between non-steroidal anti-inflammatory drug use and ovarian cancer. *Br J Clin Pharmacol.* 2013;75(1):26-35 (RR 0.94 (95% CI: 0.87-1.01) for aspirin use; RR 0.89 (95% CI: 0.74-1.08) for NSAID use); Baandrup L, Faber MT, Christensen J, et al. Nonsteroidal anti-inflammatory drugs and risk of ovarian cancer: systematic review and meta-analysis of observational studies. *Acta Obstet Gynecol Scand.* 2013;92(3):245-255 (RR 0.93 (95% CI: 0.84-1.02) for aspirin use; RR 0.94 (95% CI: 0.84-1.06) for NSAID use).

317 Trabert B, Ness RB, Lo-Ciganic WH, et al. Aspirin, nonaspirin nonsteroidal anti-inflammatory drug, and acetaminophen use and risk of invasive epithelial ovarian cancer: a pooled analysis in the Ovarian Cancer Association Consortium. *J Natl Cancer Inst.* 2014;106(2):djt431, 5 (2014) (for aspirin, OR 0.91 (95% CI: 0.84¬0.99); for NSAIDs, OR 0.90 (95% CI: 0.77-1.05)).

pharmacological research is necessary to understand the mechanisms of ovarian cancer risk reduction by aspirin use."[318] The authors reported the results of further study in 2019, continuing to find a modest decrease in risk with daily aspirin use but not with other types of anti-inflammatories, and further contradicting the inflammation theory, "observ[ing] a consistently elevated ovarian cancer risk with frequent, long-duration use of aspirin and nonaspirin NSAIDs.[319] The Wu 2009 study – on which plaintiffs' experts have relied on the issue of dose-response – likewise found the opposite effect, reporting that, "contrary to the study hypothesis that NSAIDs may have chemopreventative effects by decreasing inflammation, we found that the risk of ovarian cancer ***increased*** significantly with increasing frequency and duration of NSAIDs use."[320] And Merritt (2008) additionally found risk reduction with the use of anti-inflammatories, concluding that "on balance, chronic inflammation does not play a major role in the development of ovarian cancer."[321] Within the last few years, investigators reporting results from the PLCO Cancer Screening Trial stated that they "did not observe significant associations between aspirin use and ovarian cancer risk overall" and that "results were similar" for low-dose use, daily use and long term use (>= 10 years).[322,323] In sum, and as Dr. Smith-Bindman agrees, studies of the effect of anti-inflammatory drugs on ovarian cancer are mixed at best, and some even show the reverse relationship – i.e., increased incidence of ovarian cancer with increased use of NSAIDs.[324]

Finally, "inflammation" is a broad term and inflammation does not inevitably lead to cancer. For example, pollen can lead to increased inflammation in the asthmatic lung, but it does not cause cancer. Thus, even if one finds inflammation in tissue, that does not mean that cancer inevitably or even likely follows from that. And if talc in fact caused cancer by causing inflammation, it would surely do so in patients who undergo pleurodesis (which entails the therapeutic injection of talc into the pleural cavity to cause beneficial scarring). Yet, there is no evidence that pleurodesis patients subsequently develop cancer as a result of the procedure.

Plaintiffs' expert Dr. Ghassan Saed has performed experiments – for litigation purposes[325] – to attempt to establish an inflammation-based mechanism by which talc could cause ovarian cancer. I reviewed Dr. Saed's report, his two depositions and his testimony at the MDL *Daubert* hearing and was struck by the irregularities in his study, which render his results highly questionable. I also read the highly skeptical comments from the reviewers at

---

318 *Id.*

319 Trabert B, Poole EM, White E, et al. Analgesic Use and Ovarian Cancer Risk: An Analysis in the Ovarian Cancer Cohort Consortium, J. Nat'l Cancer Inst. 2019; 111(2):137-145, 139-142 (emphasis added).

320 Wu 2009 (emphasis added).

321 Merritt 2008.

322 Hurwitz LM, Pinsky, PF, Huang W-Y, et al. Aspirin use and ovarian cancer risk using extended follow-up of the PLCO Cancer Screening Trial. *Gynecologic Oncology*. 2020;159:522-526, at 525 and 523.

323 Hurwitz LM, Michels KA, Cook MB, et al. Associations between daily aspirin use and cancer risk across strata of major cancer risk factors in two large U.S. cohorts. *Cancer Causes & Control*. 2020; *Published online*: https://doi.org/10.1007/s10552-020-01357-2.

324 Smith-Bindman Dep. Vol. II 296:3-24 ("There doesn't seem to be a consistent message in that literature.").

325 Saed Dep. Vol. I 62:16-63:7, 72:10-73:2, 178:14-21.

Gynecologic Oncology, which rejected his manuscript.[326] His most recent publication purporting to find malignant transformation of normal epithelial ovarian cancer cells after just 72 hours of exposure to talcum powder lacks any scientific validity.[327] Comments from journal reviewers rejecting this publication stated that "the authors' conclusions suggesting acute exposure of talc powder to ovary epithelial cells is associated with ovarian cancer are outrageous and not supported by the manuscript's data,"[328] and "this paper is written in such a manner that the science cannot be trusted."[329] Further, as reviewers rejecting the publication stated, no commercial assay that purports to prove malignant transformation in just 72 hours has come close to being accepted as scientifically valid by the oncological research community.[330] It is scientifically suspect to rely on these findings as supportive evidence of plaintiffs' causal theories, but many of plaintiffs' experts cite this study as evidence of biological plausibility.[331]

THE ASBESTOS LITERATURE DOES NOT SUPPORT THE THEORY THAT ASBESTOS ALLEGED TO BE IN COSMETIC TALC COULD CAUSE OVARIAN CANCER.

There are numerous problems with plaintiffs' experts' theory that asbestos is an accessory mineral present in cosmetic talc that causes ovarian cancer.

First, all of the problems addressed above with respect to plaintiffs' theories by which particulates in talcum powder could migrate to the ovaries would apply to asbestos fibers. And any inhalation theory would be all the more infirm with respect to asbestos particularly. Assuming talc contained asbestos, the larger burden of any inhaled asbestos should be seen in the lungs, which are directly exposed, rather than the ovaries, which would only be indirectly exposed, if at all. If that is the case, we should be seeing an epidemic of mesothelioma and lung cancer cases among cosmetic talc users.[332] But no expert has identified any studies showing that mesothelioma or lung cancer is a risk of talc use, and I am not aware of any such studies. To the contrary, studies that have looked at talc miners and millers – who would presumably confront greater exposures to asbestos if it were present in talc given the occupational context – have not found any increased incidence of mesothelioma or lung cancer attributable to talc exposure in the mines or mills.[333] Notably, IARC emphasized this point, stating that there was "little or

---

326 Gynecologic Oncology Email dated Sept. 19, 2018 re: GYN-18-1020: Final Decision.

327 Harper 2023.

328 SAED_SEPT222021_SUPPL_000101.

329 SAED_SEPT222021_SUPPL_000102.

330 SAED_SEPT222021_SUPPL_000069 ("Of primary concern is the reliance on a single commercial assay for assessment of transformation that has not been established in the literature.").

331 McTiernan 2nd Am. Rep. at 83; Smith-Bindman 2nd Am. Rep. at 14; Singh Supp. Rep. at 13.

332 Wolf Dep. 345:5-346:16 ("Do I think those people should be getting mesothelioma, because I have evidence that talcum powder is contaminated with [asbestos]? I don't know. Maybe.").

333 Fiume 2015 at 119S (studies looking at occupational inhalational talc exposure do not show an increased risk of lung disease); Pira PE, Coggiola M, Ciocan C, et al. Mortality of Talc Miners and Millers from Val Chisone, Northern Italy: An Updated Cohort Study. *Journal of Occupational and Environmental Medicine*. 2017;59(7):659¬664 (concluding that there was a lack of association between exposure to asbestos-free talc, lung

inconsistent evidence of an increased risk of cancer in the studies of workers occupationally exposed to talc," where the potential for talc inhalation would be particularly significant, and that "studies of talc miners and millers were considered to provide the best source of evidence."[334] And the body of literature investigating perineal talc use has focused on ovarian cancer, and not mesothelioma or lung cancer, which indicates that researchers have not even considered them worth investigating.

In addition to the lack of a plausible mechanism by which asbestos could reach the ovaries, there is also a lack of any reliable epidemiology supporting such a causal connection. There have been relatively few studies examining the association between asbestos exposure and ovarian cancer.[335] Of the studies that have reported a statistically significant association between asbestos exposure and ovarian cancer, all looked at populations heavily exposed to asbestos in the workplace.[336] As noted by the authors of a 2011 meta-analysis that included most of this research, studies examining the asbestos-ovarian cancer association have been "limited," in part due to a "[s]mall number of cases" – i.e., "[m]uch fewer women than men have been exposed to asbestos, particularly in [the] more heavily exposed occupational settings" that have predominantly been examined.[337] Although some of these studies show a statistically significant

---

cancer, and mesothelioma in a cohort of talc miners and millers from Val Chisone, Italy); Wergeland E, Andersen A, Baerheim A. Morbidity and mortality in talc-exposed workers. *American Journal of Industrial Medicine*. 1990;17(4):505-513 (finding no elevated incidence of lung cancer or mesothelioma in a cohort or 94 talc miners and 295 talc millers).

334 IARC Talc Monographs at 412.

335 International Agency for Research on Cancer, Monographs on the Evaluation of Carcinogenic Risks to Humans Vol. 100C: Asbestos (Chrysotile, Amosite, Crocidolite, Tremolite, Actinolite, and Anthophyllite) 253 (2012) ("IARC Asbestos Monographs") (observing that "the published literature examining the association between asbestos exposure and cancer of the ovaries is relatively sparse").

336 Acheson ED, Gardner MJ, Pippard EC, Grime LP. Mortality of two groups of women who manufactured gas masks from chrysotile and crocidolite asbestos: a 40-year follow-up. Br J Ind Med. 1982; 39(4):344-348 (for gas mask workers exposed to crocidolite, SMR 2.75 (95% CI: 1.42-4.81)); Berry G, Newhouse ML, Wagner JC. Mortality from all cancers of asbestos factory workers in east London 1933-80. Occup Environ Med. 2000; 57(11):782-785 (for insulation workers, SMR 2.53 (95% CI: 1.16-4.80)); Camargo MC, Stayner LT, Straif K. Occupational exposure to asbestos and ovarian cancer: a meta-analysis. Environ Health Perspect. 2011; 119(9):1211-1217, 1216 ("Camargo 2011") (meta-analysis "restricted to highly exposed women" reporting "findings . . . consistent with the hypothesis that exposure to asbestos is associated with an increased risk of ovarian cancer"); Germani D, Belli S, Bruno C, et al. Cohort mortality study of women compensated for asbestosis in Italy. Am J Ind Med. 1999; 36(1):129-134 ("Germani 1999") (for cement works, SMR 5.40 (95% CI: 1.75-12.61); for textile works, SMR 5.26 (95% CI: 1.43-13.47); for all workers, SMR 4.77 (95% CI: 2.18-9.06)); IARC Asbestos Monographs at 256 (concluding that there is a causal association based "on five strongly positive cohort mortality studies of women with ***heavy occupational exposure*** to asbestos") (emphasis added); Magnani C, Ferrante D, Barone-Adesi F, et al. Cancer risk after cessation of asbestos exposure: a cohort study of Italian asbestos cement workers. Occup Environ Med. 2008; 65(3):164-170 (for cement factory workers, SMR 2.27 (95% CI: 1.04-4.32)); Wignall BK, Fox AJ. Mortality of female gas mask assemblers. Br J Ind Med. 1982; 39(1):34-38. ("Wignall & Fox 1982") (for gas mask workers, SMR 2.13).

337 Reid A, de Klerk N, Musk AW. Does exposure to asbestos cause ovarian cancer? A systematic literature review and meta-analysis. Cancer Epidemiol Biomarkers Prev. 2011; 20(7):1287-129, 1287 ("Reid 2011").

elevated risk, others do not, and the overall results are highly inconsistent.[338] Moreover, the meta-analysis calculated an overall standardized mortality ratio ("SMR") of 1.75 across 16 studies, which is not even a doubling of risk.[339] The SMR in these studies ranged from 0.79 in a study of Polish women diagnosed with asbestosis (in which there was only one case of ovarian cancer across 490 exposed women) to 4.77 in a study of Italian women compensated for asbestosis (nine cases of ovarian cancer in 631 exposed women).[340] Ten of the 16 studies reported SMRs lower than 2.0, none of them statistically significant.[341]

Addressing this body of research, the authors of the 2011 meta-analysis noted above acknowledged an IARC Working Group's recent conclusion that a causal association between asbestos exposure and ovarian cancer had been established,[342] but criticized that conclusion as "premature and not wholly supported by the evidence."[343] The authors also emphasized that "[s]trong evidence of consistency was not observed among these studies,"[344] pointing out that "no significant excess risk was reported among those studies that examined the incidence of ovarian cancer where cases were ascertained from a cancer registry" as opposed to from death certificates, which is significant because there is evidence of misclassification in death certificates.[345] The authors also noted that many studies involved too few women to address dose-response.[346] With respect to the studies that did address dose-response, the findings "were inconsistent"; no study showed a "statistically significant trend of ovarian cancer with degree of asbestos exposure"; and "there was no evidence of a significant trend across studies as grouped exposure increased."[347]

The authors of two 2011 meta-analyses also cautioned that to the extent there is an observed association, it may be inflated by the misclassification of other diseases such as mesothelioma as ovarian cancer on subjects' death certificates.[348] This is so because it has only

---

338 *See id.* ("The relationship between asbestos exposure and ovarian cancer is not as well understood."); *see also id.* at 1293 fig. 1 (chart showing the 16 studies, 12 of which did not report statistically significant results); *id.* at 1294 ("The present study has shown that 4 of 14 cohort studies reported a statistically significant excess rate for ovarian cancer among women exposed to asbestos. Of the remaining 10 studies, 5 reported a tendency to excess but failed to reach statistical significance and 5 reported rates that were similar to those of their reference populations. Strong evidence of consistency was not observed among these studies, although no study reported any protective effect."); IARC Asbestos Monographs at 254-56 (describing cohort studies and case-control studies).

339 Reid 2011 at 1287 (abstract).

340 *Id.* at 1289.

341 *Id.* at 1289-90.

342 IARC Asbestos Monographs at 256.

343 Reid 2011 at 1294.

344 *Id.*

345 *Id.* at 1293-94.

346 *Id.* at 1294.

347 *Id.*

348 Reid 2011 at 1287 (explaining that many studies ascertained mortality from death certificates, "[t]he accuracy of [which] has been questioned repeatedly"; observing that it has been "particularly difficult to distinguish between peritoneal mesothelioma and ovarian serous carcinoma"). Notably, this meta-analysis found that "no

recently become technologically possible to reliably "distinguish pathologically between peritoneal mesothelioma and ovarian cancer."[349] Moreover, even a low number of misclassification errors can drastically affect reported mortality rates given the limited number of ovarian cancer cases in the studies.[350] Notably, the authors of the Reid 2011 meta-analysis did not find a statistically significant ovarian cancer incidence when looking only at studies that obtained ovarian cancer diagnoses from cancer registries rather than death certificates.[351]

A recent review paper examined the historical evidence regarding asbestos and ovarian cancer in light of ongoing controversy generated by talc litigation and concluded that "it is imperative to question the International Agency for Research on Cancer's assertion that asbestos has a clear causal inference to ovarian cancer."[352] In support of this conclusion, the authors pointed to a number of factors, including: (1) the lack of reliable biological evidence to explain the development of ovarian cancer due to asbestos; (2) "the inability to review pathology and to distinguish between ovarian cancer and metastatic (pleural or peritoneal) malignant mesothelioma"; and (3) the likely use of outdated immunohistochemical techniques in the studies relied on by IARC. Given these concerns and because the "observed statistical association between asbestos and ovarian cancer . . . is weak and inconsistent,"[353] the authors concluded that "further scientific investigation is needed to clarify the causal association of asbestos and ovarian cancer."[354]

Even if IARC's conclusions were not premature, no study has found that asbestos exposure comparable to that allegedly sustained by women who use cosmetic talc causes an increased risk of ovarian cancer. The occupational studies described above include workers who worked with raw asbestos as part of their job for months or years at a time.[355] And the level of exposure is qualitatively different in the occupational context from the exposure to the genital areas alleged by plaintiffs. I am not aware of any study showing that the use of cosmetic talc would result in asbestos exposures comparable to occupational asbestos exposure even if the

---

significant excess risk was reported among those studies that examined the incidence of ovarian cancer where cases [were] ascertained from a cancer registry." *Id.* at 1294.

349 Camargo 2011 at 1216; *see id.* at 1215 (observing that earlier meta-analyses concluded that they could not reach a finding of causality despite evidence of an association because of concerns about tumor misclassification and failure to account for known risk factors).

350 Reid 2011 at 1294 ("Where disease outcome was identified from the cause of death as listed on the death certificate, given the small numbers of ovarian cancer cases in each study, even misclassification of 1 cancer may exert a large impact on the exposure effect.").

351 *Id.* ("The meta-analysis of those studies that examined ovarian cancer as determined on the death certificate reported an excess risk. In contrast, no significant excess risk was reported among those studies that examined the incidence of ovarian cancer where cases [were] ascertained from a cancer registry.").

352 Slomovitz B, de Haydu C, Taub M, et al. Asbestos and ovarian cancer: examining the historical evidence. *International Journal of Gynecological Cancer*. 2020;0:1-7, at 1.

353 *Id.* at 6.

354 *Id.*

355 Germani 1999 at 129 ("Subjects included in this cohort were certainly exposed to high levels of asbestos."); Wignall & Fox 1982 at 35 (subjects were "directly exposed to asbestos dust," and "by the end of the working day they were covered in fluff from the pads" they worked on).

cosmetic talc contained trace amounts of asbestos, as claimed by plaintiffs' experts. Thus, the results of occupational studies cannot be reliably extrapolated to exposure scenarios such as cosmetic talc use.

The results of the occupational asbestos studies also cannot be used to support causation of ovarian cancer in cosmetic talc users because the studies have predominantly examined exposure to crocidolite asbestos or some combination of crocidolite and chrysotile, and crocidolite is regarded as the most potent form of asbestos.[356] I note that studies examining the composition of talc-based body powders have not observed crocidolite fibers.[357]

Results of a cohort study of cancer incidence in women who attended a school near a large asbestos cement plant were published in 2022.[358] This study affirmed the risk of mesothelioma in women who had environmental exposure to asbestos in childhood [SIR 7.26; 95% CI 3.26-16.15]. On the other hand, the study showed the absence of risk for ovarian cancer, with an estimate of a non-significant protective effect [SIR 0.72; 95% CI 0.52-1.01].

Even assuming exposure to asbestos of some variety and in certain exposure scenarios can cause ovarian cancer, no science supports the notion – which seems implicit in plaintiffs' experts' lack of knowledge or concern regarding the doses at which asbestos exposure ostensibly poses a risk of ovarian cancer – that "any exposure" to asbestos can cause ovarian cancer.[359] To the contrary, as suggested by the discussion of occupational studies above, the available data suggest that very significant exposure would be necessary. This conclusion is strongly supported by the fact that the few studies that have looked at environmental asbestos exposure (in women living in an asbestos mining town and family members of male asbestos factory workers) rather than occupational exposure do not show a statistically significant increased rate of ovarian cancer or increased mortality from ovarian cancer.[360] For example, in one study of women who

---

[356] Reid 2011 at 1291 (noting that crocidolite is "the most mesotheliogenic of the asbestos fibers"); IARC Asbestos Monographs at 242 (discussing studies finding no excess mortality for cancer of the pharynx in amosite asbestos miners but an excess mortality rate for crocidolite miners and a higher risk rate for factory workers exposed to crocidolite than workers exposed to chrysotile); *id.* at 254-55 (relying on studies that involved crocidolite and in some cases also chrysotile).

[357] IARC Talc Monographs at 303-05.

[358] Dalsgaard SB, Würtz ET, Hansen J, Røe OD, Omland Ø. "A Cohort Study on Cancer Incidence among Women Exposed to Environmental Asbestos in Childhood with a Focus on Female Cancers, including Breast Cancer." *International Journal of Environmental Research and Public Health*. 2022;19(4):2086. Published 2022 Feb 13.

[359] *E.g.*, Wolf Dep. 168:11-169:9.

[360] Reid A, Heyworth J, de Klerk NH, Musk B. Cancer Incidence Among Women and Girls Environmentally and Occupationally Exposed to Blue Asbestos at Wittenoom, Western Australia. Int J Cancer. 2008; 122(10):2337-2344 (study of 2,552 women living in an asbestos mining town in Australia (reporting a "minimum estimate" standard incidence ratio ("SIR") of 1.11 (95% CI 0.39-1.84) and "maximum estimate" SIR of 1.43 (95% CI 0.50-2.37), depending on the method used to determine when to stop following women in the study; a standard incidence ratio reports the ratio of the number of cases of cancer found in the studied population relative to the expected number of such cases as derived from broader population statistics rather than a control group, and a standard mortality ratio ("SMR") employs a similar comparison but focuses on rates of death rather than incidence of disease); Reid A, Segal A, Heyworth JS, et al. Gynecologic and breast cancers in women after exposure to blue asbestos at Wittenoom. Cancer Epidemiol Biomarkers Prev. 2009; 18(1):140-147 ("Reid 2009") (analysis of ovarian

lived near or worked in a crocidolite mine and who had cumulative exposures of up to 40 fiber/cc-years, there was no increased risk of ovarian cancer.[361] In a pooled analysis of 21 cohorts of asbestos cement workers, there was not a significant increase in ovarian cancer overall. However, in an analysis that considered cumulative dose, there was a significant increase only in those with greater than 620 f/cc-years exposure.[362] These studies underscore the fact that even if asbestos exposure increases a woman's risk of ovarian cancer (which is still not clear) not every circumstance where there is asbestos exposure, even crocidolite exposure and even in an occupational setting, leads to elevated ovarian cancer risk.

HEALTH CANADA

Plaintiffs' experts have also relied on the recent screening assessment of talc by Health Canada ("HC").[363]

It is important to understand that the HC assessment failed to conclude that talc use causes ovarian cancer – stating only that there is a "potential" risk posed by perineal talc use[364] – and plaintiffs' experts misread the report to the extent they contend that it did.[365] Underscoring the inconclusive nature of its analysis, the assessment follows its identification of a "potential" risk with several paragraphs outlining the uncertainties in the science, citing several limitations in the animal and human studies.[366]

To the extent HC concludes that the data are "indicative" of causation, its assessment is premised on a Bradford Hill analysis that is problematic in several respects. One overarching issue is that the assessment relies extensively on reports of experts in litigation, particularly experts aligned with plaintiffs, placing them on a par with published, peer-reviewed literature and referring to all such sources interchangeably as "authors." This is an unusual approach for a neutral, scientific literature review.[367] It also draws the reliability of the review's methods into question, particularly since the HC assessment's conclusions on the individual Hill factors and on the ultimate conclusion to be drawn from them go far beyond the published, peer-reviewed literature.

---

cancer incidence in the same population (SIR 1.18 (95% CI: 0.45-1.91))); Ferrante D, Bertolotti M, Todesco A, et al. Cancer mortality and incidence of mesothelioma in a cohort of wives of asbestos workers in Casale Monferrato, Italy. Environ Health Perspect. 2007; 115(10):1401-1405 (study of family members of men employed at an asbestos-cement factory in Italy (SMR 1.42 (95% CI: 0.71-2.54)))

361 Reid 2009.

362 Luberto F, Ferrante D, Silvestri S et al. Cumulative asbestos exposure and mortality from asbestos related diseases in a pooled analysis of 21 asbestos cement cohorts in Italy. *Environmental Health* 2019; 18:71, 1-19.

363 McTiernan 2nd Am. Rep. at 86; Siemiatycki 2nd Am. Rep. at 77-78; Wolf 2nd Am. Rep. at 19-20; Smith-Bindman 2nd Am. Rep. at 30; Cote Rep. at 15-16; Plunkett 2nd Am. Rep. at 39-40, 57-58.

364 Health Canada Screening Assessment at 43 (concluding that talc use is a "potential concern for human health").

365 *E.g.*, Cote Rep. at 16.

366 Health Canada Screening Assessment at 44-45.

367 *Id.* at 29-35.

With respect to strength of association, the assessment acknowledges that the "pooled ORs from available meta-analyses," which "ranged from 1.22 to 1.35," "would not be considered' large.'"[368] In other words, the report essentially concedes that strength of association is not satisfied. Nevertheless, Health Canada goes on to find the strength factor supported because "risks of lower magnitude do not preclude a positive association and rather, may represent a low level of exposure or a rare disease," and "[o]varian cancer is recognized as a rare disease."[369] But as I have noted earlier in this report, the fact that a disease is rare does not transform every weak association involving study of rare disease into a strong one. The problems with weak point estimates remain: the association could be causal, but it could also be the result of bias or confounding – issues that the assessment later acknowledges are significant uncertainties in this context.[370]

With regard to consistency, the HC assessment generally concludes that the studies show a "high degree of consistency," even as it acknowledges that the cohort and case-control studies are generally not consistent.[371] It also downplays the results of the cohort studies, asserting for example that the cohort studies, "even when pooled together, may not be sufficiently powered" to detect a small risk.[372] But the O'Brien study – which is not mentioned in the assessment's consistency discussion – stated that it is "the largest study of this topic to date,"[373] reflecting the fact that it included more than 250,000 women, and studied participants for a median of 11 years.[374] Its size puts to rest a criticism of the talc literature offered by Narod in 2016 that more than 200,000 women would be needed to detect a 20% increased risk[375] – a statement on which the HC assessment relies in its statements about the power of the cohort studies.[376] And even prior to O'Brien, the Berge study undertook an analysis demonstrating that the cohort studies collectively had sufficient power if the true risk was 1.25; as the authors stated, "low power of cohort studies cannot be invoked as [an] explanation of the heterogeneity of results."[377] The assessment alternatively suggests that cohort studies may understate risk because of the long latency period of cancer, but fails to acknowledge that O'Brien extended the follow-up period for each of the cohort studies. In any event, as I explain earlier in this report, use of talcum powder generally starts early in life. Thus, the cohort studies are adequately designed to account for any

368 *Id.* at 29-30.

369 *Id.* at 30.

370 *Id.* at 44-45.

371 *Id.* at 33; *id.* at 31 ("Greater consistency across the different study types (cohort vs case-control designs) would increase the likelihood of a causal relationship.").

372 *Id.* at 31.

373 O'Brien 2020 at 56.

374 *Id.* at 52, Tbl 1.

375 Narod SA. "Talc and ovarian cancer." *Gynecologic Oncology*. 2016;141(3): 410-412.

376 HC Assessment at 30.

377 Berge 2018 at 253.

theorized latency in most participants. Interestingly, the assessment acknowledges the many years of follow-up, but does not explain why latency concerns should nevertheless persist.[378]

Regarding biologic gradient, the HC assessment acknowledges that "there is significant exposure information lacking to permit a fulsome assessment of biological gradient," emphasizing the difficulties in quantifying dose that I elaborated earlier in this report.[379] The HC assessment further notes that while the Taher meta-analysis (which was commissioned in connection with the HC assessment) had "isolated seven studies that provided some evidence of increased risk of ovarian cancer with increasing perineal applications of talc," "none demonstrated both a clear dose-response trend and statistical significance."[380]

With respect to biological plausibility, the HC assessment states that "a specific order of events by which perineal talc exposure could lead to ovarian cancer has not been established."[381] The assessment also relies on the McDonald 2019 study as evidence that talc can migrate, a proposition that is dubious for the reasons discussed earlier in this report, while also suggesting quite accurately that studies finding talc in ovarian tissue are not reliable because "there is a high likelihood of sample contamination without extreme measures to control it."[382] It also discusses the hypothesis that internal talc exposure may promote inflammation, which in turn may promote carcinogenesis,[383] but relies significantly on the study by Fletcher et al. that was designed and executed on behalf of plaintiffs' attorneys in talc litigation and has significant limitations, as detailed elsewhere in this report.

In short, the HC assessment employed atypical methods in the evidence it considered, and in stating only that the data are "indicative" or show a "potential" for causation, the assessment is essentially consistent with the rest of the published literature that is described above and forms the basis of my opinions.

The HC assessment also found no cancer risk from ingested talc or dermally applied talc. With regard to inhalation, it cites the Danish EPA (2016) for the conclusion that talc is "not absorbed following inhalation."[384] It points to potential for retention of talc in the lungs as leading to talc-induced pneumoconiosis or talcosis in certain industrial settings, or in some acute non-occupational settings.[385] The assessment considers the NTP rat study of inhalation (1993) of talc with doses as high as 18 mg/m^3.[386] It cites conclusions of a symposium of experts from the

---

378 HC Assessment at 32.

379 *Id.* at 33 ("[D]ata with respect to the types of powder used by subjects or the amounts applied were not presented, and therefore a relationship between the concentration/dose of talc in the powder and the incidence of ovarian cancer could not be investigated.").

380 *Id.* at 20-21.

381 *Id.* at 33.

382 *Id.*

383 *Id.* at 21.

384 *Id.* at 10.

385 *Id.* at 12.

386 *Id.* at 13.

NTP as well as academic, industry and government experts who evaluated the NTP study results and reached a consensus that because the dose was so high, the neoplasms seen were not relevant to human health risk assessment.[387] The lung tumors seen in only female rats were judged to be attributed to the general particle effects of dust, and not specific to talc, and the pheochromocytomas were attributed to tissue hypoxia, and not talc per se.[388]

THE LITERATURE DOES NOT SUPPORT THE THEORY THAT COSMETIC TALC USE COULD CAUSE UTERINE CANCER.

Based on my review of the relevant human epidemiological studies, there is no convincing evidence supporting a causal link between perineal talc use and uterine cancer. To date, there have been individual cohort studies,[389] one retrospective case-control study,[390] and one pooled analysis of four cohorts that all analyze this potential relationship.[391] None of the three cohort studies reported a statistically significant increase in risk of uterine cancer for genital ever use of talc.[392] Similarly, Neill et al. 2012, the retrospective case-control study, found no statistically significance increase in risk of endometrial cancer for ever use of talc with an OR of 0.88 (95 % CI 0.68-1.14).[393] In fact, the authors reported decreasing ORs as duration of perineal talc use increased with none of the ORs coming close to significance.[394] Most importantly, the lack of any association was confirmed by the most recent and robust analysis on this topic: Dr. O'Brien's 2021 pooled cohort analysis. This study included additional cases and follow-up data from the three previous cohort studies in addition to adding data from a fourth cohort.[395] O'Brien found a non-significant pooled HR of 1.01 (95% CI 0.94-1.09) for ever use of talc and risk of uterine cancer.[396] No significant associations were found for either long-term use

---

387 *Id.* at 14.

388 *Id.*

389 *See* Karageorgi, S., Hankinson, S. E., Kraft, P., & De Vivo, I. (2010). Reproductive factors and postmenopausal hormone use in relation to endometrial cancer risk in the Nurses' Health Study cohort 1976–2004. *International Journal of Cancer,* 126(1), 208-216 ("Karageorgi 2010"); Crawford, L., Reeves, K. W., Luisi, N., Balasubramanian, R., & Sturgeon, S. R. (2012). Perineal powder use and risk of endometrial cancer in postmenopausal women. *Cancer Causes & Control*, 23(10), 1673-1680 ("Crawford 2012"); O'Brien KM, D'Aloisio AA, Shi M, Murphy JD, Sandler DP, Weinberg CR. Perineal Talc Use, Douching, and the Risk of Uterine Cancer. *Epidemiology*. 2019 Nov;30(6):845-852 ("O'Brien 2019"); O'Brien 2024.

390 *See* Neill, A. S., Nagle, C. M., Spurdle, A. B., & Webb, P. M. (2012). Use of talcum powder and endometrial cancer risk. *Cancer Causes & Control*, 23(3), 513-519 ("Neill 2012").

391 *See* O'Brien, K. M., Tworoger, S. S., Harris, H. R., Trabert, B., Weinberg, C. R., Fortner, R. T., ... & Sandler, D. P. (2021). Genital powder use and risk of uterine cancer: A pooled analysis of prospective studies. *International Journal of Cancer*, 148(11), 2692-2701 ("O'Brien 2021").

392 *See* Karageorgi 2010 at Table 2 (RR = 1.13, 95% CI 0.96-1.33); Crawford 2012 at Table 2 (HR = 1.06, 95% CI 0.87-1.28); O'Brien 2019 at Table 2 (HR = 1.2, 95% CI 0.94-1.6).

393 Neill 2012 at Table 2.

394 *See id.*

395 *See* O'Brien 2021 at Table 1.

396 *See id.* at Table 2.

(HR = 1.12, 95% CI 0.96-1.31) or frequent use (HR = 1.05, 95% CI 0.95-1.16).[397] When confined to medically-confirmed uterine cancer, the association fell to 1.00 exactly.[398]

CONCLUSION

It is my opinion, based on my qualifications and my extensive review of the available epidemiology studies and scientific literature, that there is not sufficient evidence to conclude that there is a causal relationship between perineal talcum powder exposure and ovarian cancer (including borderline serous OC). The epidemiologic literature shows a non-existent association or, at most, a small association between perineal talc use and ovarian cancer (including borderline serous OC) that constitutes only weak epidemiologic evidence that can be attributed to bias, confounding or chance. The studies are inconsistent across study designs and within study designs, as cohort and hospital-based case-control studies do not show a statistically significant association and only a subset of the population-based case-control studies demonstrate a statistically significant association. Moreover, the case-control studies do not show any consistent evidence of a dose-response relationship, and there is a complete lack of evidence for dose-response in the cohort studies. The theories pertaining to biological plausibility are entirely speculative and have not been demonstrated in the epidemiology studies or scientific literature; rather, relevant science contradicts the purported theories of talcum powder transport and development of ovarian cancer by inflammation. Finally, the assertion that asbestos present in talc – even if true – causes ovarian cancer is problematic on the grounds that there is a lack of a plausible mechanism by which asbestos could reach the ovaries and also a lack of any reliable epidemiology supporting such a causal connection.

All of the opinions in this report are stated to a reasonable degree of scientific certainty.

397 *See id.*

398 *See id.* at Table 3.